Anti-ageing medicine
Myths and chances

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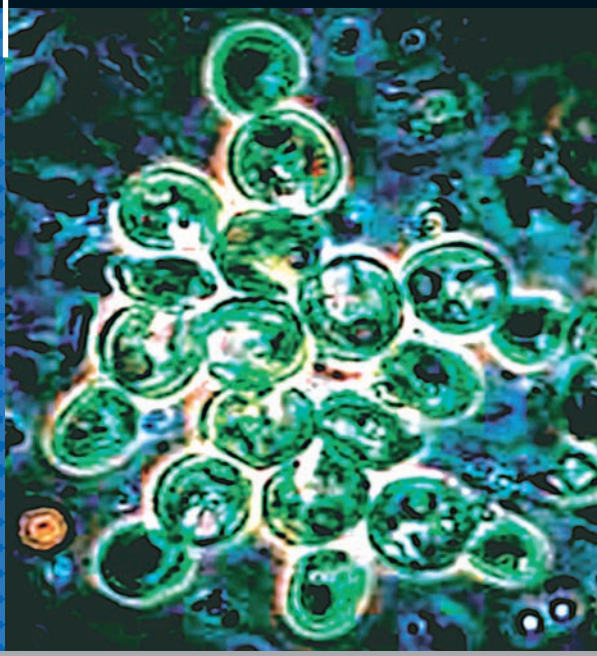

Astrid Stuckelberger

Anti-Ageing Medicine: Myths and Chances

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Dr Astrid Stuckelberger

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with the collaboration of
Prof. Philippe Wanner

and the contributions of
Dr Kaweh Mansouri,
Dr Leslie Olson,
Barbara So-Barazetti and
Dr Markus Zimmermann-Acklin

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TA-SWISS
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CH-3003 Bern
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Executive Summary

The composition of our society is changing. The proportion and absolute numbers of older people are increasing worldwide. The elderly population has already exceeded the child population (below age 15) and by 2050, for every child there will be two elderly persons. This shift, which has come to be known as 'demographic transition', has far-reaching consequences. Old people have different expectations then younger generations and with each generation of older persons comes different ways of life. Up to now, society has been oriented towards youth, but this trend is changing: the growing number of people who are now classified as senior citizens is a powerful force for change. This development is due to the fact that on average, people tend to live longer than ever before and in good health. Furthermore, these people want to retain their youthful vigour and their vitality for as long as possible resisting any signs of deterioration. It is well known that the Baby Boom Generation attaches more importance than any previous generation to postponing or halting the process of ageing and all its ailments. Besides, recent scientific and technological progress have contributed to significant medical advances in preventing or rehabilitating a range of age-related diseases and incapacities, giving evidence to the claims that ageing 'successfully' is possible. That is the niche that anti-ageing medicine occupies. There have been extraordinary developments over the last ten to fifteen years; the methods range from established medical procedures to developments in biotechnological interventions, bioengineered or robotic solutions, onto applications classified more as cosmetic care and mental training.

The aim of this TA-SWISS study is to formulate an overview of the possibilities and risks of individual anti-ageing medicine, based on scientific evidence with a view to encouraging a wide discussion on an issue that every one of us will have to deal with at some time or other.

The objective of anti-ageing is to give people the possibility of enjoying an optimal quality of life in old age via technology and raising even further life expectancy. It is not the concept of normal ageing that is the focus of anti-ageing medicine, but rather the idea of ageing successfully while maximising performance. The problems of old age should be prevented as early as possible, so that the impairment that comes with advancing years does not

happen at all. The main emphasis is on early prevention and early detection at any age. The intention is to preserve fitness from an early stage, for instance with vitamins and hormones. If injuries or deterioration do occur, they should as far as possible be 'repaired' through medical, bionic or cosmetic interventions. Elderly people suffering from incapacities should be given electronic aids or robots to improve their quality of life. According to the definition of the founders of anti-ageing medicine, "anti-ageing medicine is a medical speciality founded on the application of advanced scientific and medical technologies for the early detection, prevention, treatment and reversal of age-related dysfunction, disorders, and diseases".

At present, the possibilities of anti-ageing are promising yet many are still either at the experimental stage or only theoretical. While there is a range of medical procedures which are clinically applied today, others are only hope for the future. They include those that can be used to repair damage to the heart for instance or stem cell treatment. Depending on the application, these procedures are either at the laboratory and animal testing stage, or at the clinical practice phase with only very few undergoing clinical trials. Many of them are not of practical help to the general population, but are applied only to specific cases. Age-related eye diseases follow a similar pattern: while retina can already be made with stem cells, other interventions using prostheses to restore eyesight to the blind are still at the experimental level. Some methods, such as the reinforcement or replacement of cartilage cells, are available in practice, enabling joints that have become useless because of wear and tear to be saved and the function restored, rather than turning to artificial ones.

Many active substances, such as hormones and vitamins, have become part of everyday life and are today developing through a whole range of products and fortified food. So although this has created an extremely lucrative market and despite the positive results, the impact of anti-ageing medicine on successful ageing has not yet been thoroughly studied. While in many cases the use of theses substances is not harmful, there are others, such as hormone replacement therapies, which pose a contradictory risk-benefit dilemma to health. It is unclear whether anti-ageing medicine as a whole contributes to improving the ageing process in general, or whether its benefits are limited to individual cases according to case indications.
The characteristics of anti-ageing medicine are that: (i) in many cases the evidence for its effectiveness is not fully proven by well conducted randomised clinical trials, (ii) not all new possibilities of intervention are utilised to treat

injuries or for prevention, and (iii) despite its growing importance, the market is not controlled. These three areas require further studies. Concerning the first point, the TA-SWISS study concludes that better studies on the effectiveness of these methods and products are required, as also further control on the dangers and risks of anti-ageing medical practice and devices. Consumers' interest, at any age, is at stake—because certain methods used may create a danger if they are carried out by unqualified staff or with untested technological devices. Medical practitioners are in a better position to evaluate the successfulness of the treatment according to individual condition (biological age, gender, health condition), thus offering a new type of 'tailor-made' medicine, which requires the adaptation of continuous medical education. The second point is that the rapid transfer of scientific findings to quality products and interventions for anti-ageing needs improvement through communication and coordination. For the third point, we need a stringent system of quality and safety control for new procedures that must be combined with compulsory labelling. In this case, however, it is important to bear in mind the international dimension of the market for anti-ageing preparations: Switzerland has to consider how European and international regulations can respond to safety measures corresponding to the transnational dimension of the anti-ageing market.

Résumé

Les composantes de notre société changent. Partout dans le monde, le nombre de personnes âgées augmente, tant proportionnellement qu'en chiffres absolus. La population âgée a déjà dépassé la population des jeunes de moins de 15 ans et en 2050, on s'attend à voir un enfant par 2 personnes âgées. Cette "transition démographique" – selon le terme consacré – aura des conséquences de vaste portée. Les personnes vieillissantes ont d'autres exigences et chaque génération vieillit avec ses spécificités propres. La société ne pourra plus, comme c'est encore le cas, être tournée vers la jeune génération, ne serait-ce que du fait du nombre croissant de seniors qui constitue un puissant moteur de changement. Une des causes indéniables de cette évolution est que l'espérance de vie en bonne santé ne cesse d'augmenter. Qui plus est, les gens aspirent désormais à conserver la fraîcheur et la vitalité de leur jeunesse aussi longtemps que possible et sont de ce fait disposés à lutter contre les signes de dégénérescence. La génération du baby-boom en particulier tient à repousser tant que faire se peut l'apparition de la vieillesse et de son cortège de maux. En parallèle, les progrès scientifiques et technologiques récents on contribué de façon significative aux avancées médicales, notamment dans la

prévention ou la réhabilitation d'une série de maladies et incapacités liées à l'âge, prouvant de ce fait que le vieillissement peut être vécu avec succès, en pleine autonomie et en bonne santé. Et c'est sur le créneau créé par cette aspiration que la médecine antivieillissement a pris position et connaît un énorme développement depuis dix à quinze ans. Les solutions proposées relèvent aussi bien des pratiques éprouvées de la médecine classique, des interventions biotechnologiques de pointe ou des avancées de la robotique que de la cosmétique ou de l'entraînement cérébral.

Mandatée dans ce but, l'étude de TA-SWISS résumée ici donne un aperçu de l'évidence scientifique sur les possibilités et les risques des différents moyens de lutte contre les signes et maladies du vieillissement. Elle a pour objectif de servir d'incitation et de point d'ancrage à une large discussion sur un sujet qui, tôt ou tard, nous concernera tous.

La médecine antivieillissement, dite aussi 'anti-âge', a pour objectif de permettre aux gens d'avancer en âge tout en conservant une qualité de vie optimale et en augmentant son espérance de vie en santé. En d'autres termes, cette médecine ne se focalise pas sur le vieillissement normal, mais sur sa réussite : les maux engendrés par l'âge doivent être évités, tout comme l'apparition des signes de décrépitude. La prévention est donc de prime importance, quel que soit l'âge. La médecine anti-âge cherche soit à assurer le renforcement et le maintien des fonctions et des performances de la jeunesse, par exemple, par la prescription précoce de vitamines et d'hormones ou soit, si des détériorations se sont déjà produites, à y remédier dans toute la mesure du possible par des interventions médicales, bioniques ou esthétiques. Et, lorsque le vieillissement ne peut plus être enrayé, elle tente encore d'améliorer la qualité de vie en proposant des aides électroniques et des robots. La médecine antivieillissement est donc, selon la définition de ses fondateurs, "une spécialisation qui repose sur l'utilisation de technologies scientifiques et médicales de pointe appliquées à la détection précoce, la prévention, le traitement et la régression des maladies, des incapacités et des troubles fonctionnels dus à l'âge."

Pour l'heure, les possibilités de lutte contre le vieillissement sont encourageantes bien que nombreuses sont celles qui sont au stade expérimental ou théorique. Alors qu'il existe une série de procédures médicales déjà appliquées au cas par cas au niveau clinique, le développement de toute une panoplie de traitements soulève actuellement de grands espoirs. Y figurent notamment ceux

susceptibles de remédier à des lésions cardiaques et les traitements par les cellules souches. Selon l'application envisagée, ces traitements en sont encore au stade de la recherche en laboratoire ou de l'expérimentation animale et, dans d'autres cas, en phase de test clinique avec de petits échantillons avant d'être menées à de plus grandes échelles. Autrement dit, nombre d'interventions sont utiles individuellement mais encore éloignées d'une utilisation pratique généralisable au service de l'être humain. Il en va sensiblement de même pour les maladies ophtalmologiques liées à l'âge : alors que la rétine peut déjà être produite à partir de cellules souches avec succès, d'autres interventions avec de nouvelles prothèses appelées à redonner une perception visuelle aux personnes aveugles sont encore à l'état expérimental. Parmi les interventions déjà disponibles cliniquement figure le recours à des traitements pour renforcer ou remplacer les cellules cartilagineuses pour préserver des articulations et restaurer la fonctionnalité que l'usure avait rendu inutilisables et éviter ainsi la mise en place de prothèses.

Pour ce qui est de la vie quotidienne, une multitude de substances actives – notamment des hormones ou vitamines de synthèse – ont fait leur apparition dans la vie quotidienne et même dans la nourriture dite 'fortifiée'. Ces développements ont fait naître un marché extrêmement lucratif sans que le rôle bénéfique de ces substances dans le processus de vieillissement n'ait pu être encore systématiquement prouvé à large échelle. À tout le moins, leur utilisation est dans bien des cas inoffensive, mais il y a aussi des exceptions, telles les thérapies hormonales substitutives, qui comportent un réel dilemme risque-bénéfice sur la santé. En bref, l'on ne saurait encore dire si la médecine contre le vieillissement contribuera de manière fondamentale à l'amélioration générale du processus ou si ses interventions se limiteront à des indications particulières de cas en cas.

La médecine antivieillissement se distingue par le fait (i) qu'il n'existe souvent pas d'évidence systématique et généralisable de son efficacité s'appuyant sur des études randomisées, (ii) que tout le potentiel des nouvelles interventions préventives ou réparatrices n'est pas encore utilisé et (iii) que, malgré son ampleur, le marché grandissant qu'elle constitue n'est pas surveillé. Des interventions dans ces trois domaines s'imposent. Concernant le premier point, l'étude de TA-SWISS conclut à la nécessité de mener des recherches plus poussées non seulement sur les effets bénéfiques, mais aussi sur les dangers et les risques de la médecine antivieillissement et des outils technologiques utilisés. Des mécanismes de contrôles de qualité doivent être poursuivis dans

l'intérêt de la sécurité des consommateurs et des consommatrices de tout âge, car certains des procédés que la médecine anti-âge utilise peuvent être hasardeux pour la santé lorsqu'ils sont, par exemple, appliqués par du personnel non qualifié ou avec des instruments technologiques non vérifiés. De leur côté, les médecins peuvent mieux évaluer les chances de succès des différentes solutions envisageables dessinées selon les conditions de chaque individu (âge biologique, sexe, état de santé) et d'élaborer en quelque sorte une médecine anti-âge sur mesure, d'où l'importance d'une formation continue adaptée. Deuxième point: le transfert rapide des nouvelles découvertes scientifiques aux interventions et dans l'élaboration de produits contre le vieillissement réclame une meilleure communication et coordination. Et pour ce qui est du troisième point, il s'agit d'instaurer un contrôle rigoureux de la qualité et de la sûreté des nouvelles méthodes et de le lier à l'obtention obligatoire d'un label ou d'une formation. Cela ne saurait toutefois se faire sans tenir compte de la diffusion internationale des produits contre le vieillissement. Vu que le marché antivieillissement est rapidement devenu international et transnational, la Suisse doit se concerter au niveau européen et international pour convenir d'une régulation adaptée.

Zusammenfassung

Die Zusammensetzung unserer Gesellschaft ändert sich. Der Bevölkerungsanteil der Älteren und ihre absolute Zahl nehmen weltweit zu. Die ältere Bevölkerung hat bereits die Kinder (unter 15 Jahren) überholt, und im Jahr 2050 werden auf jedes Kind zwei Senioren kommen. Diese Veränderung – auch "Demografischer Wandel" genannt – hat weitreichende Auswirkungen. Alte Menschen haben andere Ansprüche, und mit jeder Generation ändert sich auch ihr Lebensstil. Unsere Gesellschaft wird sich nicht mehr wie bisher auf die Jugend konzentrieren können, da die Älteren allein schon durch ihre wachsende Anzahl ein kraftvoller Antrieb für den Wandel darstellen. Diese Entwicklung beruht auf der Tatsache, dass Menschen durchschnittlich älter werden und auch im hohen Alter gesunder bleiben als je zuvor. Dazu kommt, dass die Alternden sich die jugendliche Frische und Vitalität so lange wie möglich erhalten möchte und die Zeichen des Verschleisses bekämpft. Gerade die Generation der Babyboomer mehr legt Wert darauf als jede Generation vor ihr, den Prozess des Alterns und alle damit verbundenen Beschwerden so lange wie möglich hinauszuzögern. Darüber hinaus haben jüngste wissenschaftliche und technologische Entwicklungen zu signifikanten medizinischen

Fortschritten bei der Vorbeugung und der Rehabilitation einer Anzahl altersbedingter Krankheiten und Gebrechen beigetragen, was zur Behauptung geführt hat, dass ‘erfolgreiches Altern’ möglich sei. Diese Nische bedient die Anti-Ageing-Medizin und konnte in den letzten zehn bis fünfzehn Jahren eine enorme Entwicklung durchmachen. Die angebotenen Methoden reichen von etablierten medizinischen Verfahren über biotechnologische Interventionen und Entwicklungen der Robotertechnik (Robotik) bis hin zu kosmetischen Anwendungen und Techniken des Mentaltrainings.

Ziel der vorliegenden TA-SWISS Studie ist es, einen Überblick über die medizinisch erwiesenen Möglichkeiten und Risiken der einzelnen Anti-Ageing-Methoden zu geben, um eine breite Diskussion zu diesem Thema anzuregen, das jeden von uns einmal betreffen wird.

Die Anti-Ageing-Medizin soll Menschen ermöglichen, auch im Alter eine optimale Lebensqualität zu bewahren, und Methoden finden, die Lebenserwartung gar noch zu erhöhen. Das Hauptaugenmerk von Anti-Ageing liegt demnach nicht das normale Altern, sondern das ‘erfolgreiche’ Altern bei höchstmöglicher Leistungsfähigkeit: Den Altersbeschwerden soll so früh wie möglich entgegengewirkt werden, sodass Gebrechen, die mit voranschreitendem Alter auftreten, ebenfalls ausbleiben. Ungeachtet des Alters kommt dabei der Prävention sowie der Früherkennung der grösste Stellenwert zu. Bereits frühzeitig soll die Leistungsfähigkeit, beispielsweise durch Verabreichung von Vitaminen und Hormonen, gesichert werden. Wenn dennoch Schädigungen oder Verschleiss auftreten, sollen sie soweit möglich mit medizinischen oder kosmetischen Eingriffen ‘repariert’ werden. Grundlegend beeinträchtigte ältere Personen schliesslich erhalten elektronische Hilfsmittel oder Roboter zur Verbesserung ihrer Lebensqualität. Die Anti-Ageing-Medizin ist gemäss der Definition ihrer Erfinder “eine auf fortschrittlichen wissenschaftlichen und medizinischen Technologien beruhende medizinische Teildisziplin, die zur Früherkennung, Prävention, Behandlung und Bekämpfung von altersbedingten Funktionsstörungen, Behinderungen und Krankheiten eingesetzt wird.”

Viele der Möglichkeiten von Anti-Ageing sind derzeit zwar vielversprechend, aber noch im Entwicklungsstadium oder rein theoretischer Natur. Während es eine Reihe von medizinischen Verfahren gibt, die schon klinisch angewendet werden, geben andere Anlass zur Hoffnung für zukünftige Generationen. Dazu gehören beispielsweise die Stammzellentherapie und Methoden, mit denen

Schädigungen – zum Beispiel am Herzen – behoben werden könnten. Je nach geplanter Verwendung befinden sich diese Verfahren erst in der Phase der Labor- und Tierversuche, im klinischen Versuch und nur in ganz wenigen Fällen bereits in klinischen Studien. Viele werden in Einzelfällen angewendet, sind aber noch lange nicht der allgemeine Bevölkerung zugänglich. Ähnliches gilt für altersbedingten Augenerkrankungen: während Retinazellen schon aus Stammzellen gewonnen werden können, befinden sich Prothesen zur Wiederherstellung der Sehkraft bei Blinden noch auf einer sehr experimentellen Stufe. Dagegen finden Vermehrung und Ersatz von Knorpelzellen bereits in der Praxis Anwendung, um durch Verschleiss unbrauchbar gewordene Gelenke wiederherzustellen und sie nicht durch künstliche ersetzen zu müssen.

Eine Vielzahl von Wirkstoffen wie Hormone und Vitamine hat in den Alltag Einzug gehalten und sind auch in einer ganzen Spanne von angereicherten Nahrungsmitteln anzutreffen. Trotz dieses äusserst lukrativen Marktes und der positiven Ergebnisse konnten ihre Auswirkungen auf ein erfolgreiches Altern noch nicht erschöpfend nachgewiesen werden. Während in vielen Fällen ihre Verwendung zumindest nicht schädlich ist, stellen einige Wirkstoffe, wie zum Beispiel Hormonersatztherapien, vor ein gesundheitliches Risiko-Nutzen-Dilemma. Es wird sich zeigen, ob die Anti-Ageing-Medizin zu einer umfassenden Verbesserung des Alterungsprozesses eingesetzt oder ob ihr Nutzen sich auf individuelle, fallweise Anwendung beschränken wird.

Die Anti-Ageing-Medizin unterscheidet sich von der klassischen Medizin insofern, (i) dass in vielen Fällen der Beweis für ihre Wirksamkeit durch sorgfältig durchgeführte randomisierte klinische Studien noch nicht erbracht wurde, (ii) dass nicht alle neuen Möglichkeiten der Intervention schon bei Schädigungen und zur Prävention genutzt werden, und (iii) dass trotz ihrer zunehmenden Verbreitung der wachsende Markt nicht kontrolliert wird. Auf allen drei Gebieten muss in Zukunft etwas getan werden. Den ersten Punkt betreffend kommt die TA-SWISS-Studie zu dem Schluss, dass es nicht nur bessere Studien über die Wirksamkeit, sondern auch eine bessere Kontrolle der Gefahren und Risiken der Anti-Ageing-Medizin und -Verfahren geben muss. Derartige Behandlungen können Konsumentinnen und Konsumenten aller Altersgruppen ernstlich gefährdet werden, wenn sie von unqualifiziertem Personal oder mittels nicht ausgetesteten technologischen Hilfsmitteln angewandt werden. Einzig ausgebildete Ärzte sind in der Lage, die Erfolgsaussichten einer Behandlung unter Berücksichtigung der persönlichen Kondition (biologisches Alter, Geschlecht und Gesundheitsverfassung) ein-

zuschätzen, was auch den Ruf nach medizinischer Weiterbildung auf dem Gebiet laut werden lässt. Zu Punkt zwei (ii): Für einen schnellen Transfer wissenschaftlicher Erkenntnisse bei Anti-Ageing-Produkten und -Verfahren braucht es bessere Kommunikation und Koordination. Was den dritten Punkt betrifft, ist eine strenge Qualitäts- und Sicherheitsprüfung von neuen Verfahren nötig, die mit einer Kennzeichnungspflicht zu kombinieren ist. Gerade weil der Markt der Anti-Ageing-Präparate ein internationaler und länderübergreifender ist, muss die Schweiz ihre Sicherheitsbestimmungen und Kontrollmechanismen auch mit europäischen und internationalen Bestimmungen abstimmen.

Editorial Note

The language adopted in the book is English U.K.

The currencies are marked as CHF for Swiss francs, Euros, and $ for U.S. dollars.

A Glossary of technical terms is included in chapter 13.

Abbreviations will be cited once and used throughout the document. The most frequent abbreviations are listed below.

List of main abbreviations

AAM	Anti-Ageing Medicine
A4M	American Academy for Anti-Aging Medicine
EPFL	Swiss Federal Institute of Technology in Lausanne
ETHZ	Swiss Federal Institute of Technology in Zurich
EC	European Commission
EU	European Union
FDA	Food and Drugs Administration in the United States
OECD	Organisation for Economic Co-operation and Development
OFAS	Swiss Federal Social Insurance Office
SECO	State Secretariat for Economic Affairs
SFOPH	Swiss Federal Office of Public Health
USDA	United States Department of Agriculture
WHO	World Health Organisation

1. Introduction

1.1. The Challenge of Time

The unprecedented increase in longevity, the continuous progress in medicine and technologies and the continuous rise in the number and proportion of older persons have brought new challenges and opportunities to society and policymakers. Older persons not only live longer than their ascendants, they also progressively participate in a new 'Long Life Society', very different from the society we know today.

The challenge of a 'long life society' is to ensure that the years gained with a higher life expectancy are not only healthy and disability-free years, but are years offering a good quality of life. In this perspective, recent research has concentrated on identifying the factors contributing rather than hindering the healthy ageing process. Evidence based new models of "optimal ageing" (Baltes and Baltes, 1990; Baltes, 1997) or 'successful ageing' (Rowe and Kahn, 1997, 1998) have now been established in opposition to the traditional decline models of ageing.

Striving to extend human life to its highest limit is reflected in what is called 'longevity' medicine" or 'prolongevity' and which has been also called 'anti-ageing medicine'. Advances in all aspects of medicine, especially in the fundamental metabolic and functional process of ageing have led to new findings susceptible of transforming the traditional concept of physiological decline with age. Today, research in the prevention and treatment of ageing symptoms has reached a point where a new paradigm of human development is about to be offered: reversal of some of the ageing symptoms, control of different ageing-related illnesses, regeneration processes, human enhancement and replacement of different body parts are possible. The findings and data are proliferating along with a growing market for anti-ageing medicine and products.

The 'anti-ageing' movement claims many unprecedented features to combat the symptoms of ageing: to slow down the ageing process, to enhance health and vitality, to increase life expectancy and ultimately to improve the quality of life of older persons and thus of society as a whole. Two tendencies are included in

the anti-ageing movement: (i) the practice of preventive ageing medicine using a large area of interventions, and (ii) the promotion of promising solutions, offered by life science biotechnologies and scientific progress to consumers of all ages, often despite systematic evidence. The most optimistic and futuristic train of thought which many academics oppose even suggests that bio-technological progress and findings will not only slow down the process of ageing, but would stop or even reverse it.

Definition of Anti-ageing Medicine

Anti-ageing interventions, known as 'anti-ageing medicine', are measures intended to slow, arrest, and reverse phenomena associated with ageing and to extend the human life span.

(Adapted from Robert H. Binstock:
Anti-ageing Medicine: the History, 2004:523–533)

A good quality of life during old age is an objective that many strive to attain. Although the wide range of research conducted the two decades on the factors contributing or hindering quality of life, many questions remain unanswered. In particular, the degree of scientific consensus between anti-ageing specialists and those who are against such medicine is very low and it is very difficult to weigh the different point of views. For a wide range of AAM products, not only are the effects poorly verified (or verified only on animals in laboratories but not on humans), but the immediate and long-term risks are not known. At the same time, the number and the diversity of AAM products and care rapidly increase. Such products are available among the public and are widely sold using commercial methods with almost no control, for instance by internet platforms.
For a long time, the AAM was dominated by a grey market with small producers of hormones or dietary supplements distributing their products through unofficial distribution channels. We want to remain young and this dream boosts the market.

But now, a high potential development of AM products is emerging, with the participation of well-known multinationals (e.g. *Nestlé*, etc.) aiming at taking the lead on some segments such as brain food or micro-nutrients. In 2007, *Nestlé* announced that it bought the nutrient sector of *Novartis* to be the world number

two in the sector of health nutrient.[1] At the beginning of 2007, *PepsiCo* reported on merger talks with *Nestlé* to be involved in healthy food production. Today, we witness the trading in medicine not only in clinical practice but even more in the industrial sector. The consumer is particularly responsive to the blooming trend to sell health, beauty and anti-ageing products and practices.

Behind this commercial scene, substantive investments are involved in life science research which could offer innovative solutions to fight age-related disorders and disabilities, but also to increase life-long performance and autonomy. AAM is not only a commercial trend, but also an opportunity for society to increase the quality of life of a growing ageing population.

This report strives to bring clarity to the issue of anti-ageing medicine, not only based on present day evidence in anti-ageing interventions but also on its societal impact. The latest knowledge and evidence will be provided on the benefits vs. risks, the safety and regulations, but also the ethical issues linked to AAM. Recommendations will be made for researchers, practitioners and policymakers.

1.2. Objectives

The main and first objective of the project is to shed an interdisciplinary light on the so-called 'anti-ageing' medicine and its current development in a 'long life society'; secondly, the project aims at describing the medical and social consequences of the anticipated technological advances in medicine.

More specifically, two aspects of this project are of importance: on one hand to bring information on the preventive measures and interventions that are currently recognised for slowing down the aging process and improving the disability-free life expectancy, and on the other hand, to explore the technological progress that is taking place in preventing pathological ageing and enhancing a better life. In the latter aspect, evidence-based findings in ageing prevention for better ageing and anti-ageing medicine will be the first concern.

[1] Nestlé Nutrition is made up of three segments: Healthcare Nutrition, which includes protein drinks and other dietary supplements, Performance Nutrition, which includes low-calorie energy bars, and Infant Nutrition. See News on Forbes.com, 4.12.2007, "Analysts Applaud Nestlé's Gerber Acquisition" by Parmy Olson, http://www.forbes.com/2007/04/12/nestle-gerber-novartis-markets-equity-cx_po_0412markets02.html

Another objective will be to distinguish as far as possible, at this point in time, between what can be called the “grey area” and the inconsistent and false promises. General key objectives moreover include explaining the aims of the AAM movement, to describe the anti-ageing market in Switzerland and identify possible ethical issues. Finally, the project aims at formulating recommendations for decision-makers and politicians.

According to the objectives, the focus is not on providing a systematic review of life science technological interventions of anti-ageing experimentation and research done on animals and humans; but the project synthesises the existing, emerging or missing evidence on a selection of molecules, products and interventions. It systematically recognises the differences between ‘anti-ageing’ and ‘better ageing’ approaches. It also identifies the gaps where more knowledge is needed, as well as where devices and products need to be more closely scrutinised and controlled for public safety.

2. Methods

2.1. Context and Theories on Ageing

Theories of ageing have emerged in parallel to medical, demographic and economic development. The review of the demographic situation given at the beginning of chapter 3 aims at providing an approximate description of the future of the AAM market. Given the increase in the number of elderly and the regular progress of their socio-economic situation, it is expected that the AAM market will benefit from great opportunities. In the same chapter, general theories on ageing stemming from medical and social sciences will give the context in which biological theories on ageing, many of which are anti-aging medicine related, have flourished. The theories will be followed by a more detailed analysis of the two subsequent trends covered here—'Better Ageing' and 'Anti-ageing'—their main basis, current developments and issues debated today are presented.

The method used to analyze anti-ageing medicine is adapted to the fact that it is a new subject with developments into clinical practice and consumership which are not available solely in scientific literature. For this purpose 4 approaches allowed to build theoretical, scientific and practical evidence:

Table 1: Synopsis of the Anti-Ageing Medicine Study

3 TYPE OF SURVEYS	SCIENTIFIC REVIEWS
AGEING EXPERT SURVEY International and National Expert Networks -Panels of experts in aging -Questionnaire (open/closed questions) -120 experts contacted in the world (2/3 responded, 55 questionnaires)	**SCIENTIFIC STATE OF THE ART** **SCIENTIFIC REVIEW** Meta-analysis, systematic reviews and thematic reviews
FACE-TO-FACE IN-DEPTH INTERVIEW with AAM and Longevity protagonists -AAM founders -International longevity center founders -AAM-linked experts -Questionnaire guideline for interviews	**EXPERT MANDATES** Socio-ecological, AAM case studies (ophtalmology, dentistry), economic and ethics expert review and consultation
AAM PRACTICE SURVEY: **CLINICS, PRIVATE PRACTICE & INDUSTRY** -AAM clinics and practitioners -AAM-related industry -Questionnaire guideline for interviews in Switzerland and Japan	**PRESS REVIEW** Scientific press review, scientific press release, technologial awards, AAM publications and websites

2.2. Review of Existing Literature

Through a review of the literature (state-of-the-art), the report lists preventive measures and studies the evidence on better and healthier ageing as well as on anti-ageing medicine, with a two level approach:

I. *Safe evidence on better and healthier ageing* (chapter 4): review of determinants and interventions to promote better and healthier ageing preventing diseases and loss of function in old age, which have reached a large consensus through consistent and repeated scientific findings over the years.

II. *Risk-related evidence ranging from 'probable' to 'inconsistent', 'non conclusive' or 'high risk'* (chapter 5): review of more controversial and less consistent findings on new interventions, such as biomedical or technology-related interventions to prevent age-related signs and symptoms with attempts to 'slow, arrest, or reverse the ageing process'. Those interventions are often called 'preventive ageing' or 'anti-ageing' medicine and are based much more on theories of ageing allowing the possibility of extending longevity or distinguishing between those metabolic elements that age and those that do not age.

The state-of-the-art covers the factors that have an effect and those that have no influence on either side of ageing processes:

a) *Better and healthier ageing:* a vast literature, both traditional and recent, is synthesised from scientific articles and books, from government and/or expert documents and WHO technical reports

b) *'Anti-ageing' interventions to 'slow, arrest, or reverse the process of ageing':* given that, on one hand, the subject is recent and includes a vast array of interventions and measures from biomolecular levels to surgery, and that, on the other hand, the survey and report shows scarce consensus among experts and even contradictory findings in peer-review articles for the same product or interventions; the analysis mainly takes into consideration literature reviews, systematic reviews, meta-analysis and available data

A systematic approach was taken by identifying the most prominent findings of the major databases in peer-review journals. The literature and articles included in this report are drawn from databases such as Cochrane and PubMed and also stem predominantly from English written documents, (although, relevant German and French papers were also selected for specific findings). This search was complemented by other sources such as international agencies and programmes (the United Nations programme on Ageing, World Health Organisation), governmental agencies (National Institutes on Health or on Ageing) or inter-governmental agencies (OECD,[1] European Commission), and academic institutions. In Switzerland, documents from the Swiss Office of Public Health and Swiss Health Observatory (Obsan), Swissmedic[2] as well as medical and para-medical specialised associations, patient and consumer organisations were also included.

2.3. Consultation on International and National Expert Knowledge[3]

This consultation was conducted through a pluralistic approach including:

- *Expert opinion surveys* through an open-ended questionnaire distributed via mail and e-mail to expert networks.

- *Face-to-face interviews* with specialists of longevity, ageing and/or anti-ageing. These interviews used guidelines and were recorded and rewritten for analysis.

- *On-site and online clinical visits and interviews in Switzerland and Japan* to describe current practice, the local AAM market and the expected development of AAM.

[1] OECD: Organisation for Economic Co-operation and Development – www.oecd.org

[2] Swissmedic: the Swiss Agency for therapeutic products, part of the Department of Home Affairs, which aims at protecting humans and animals by ensuring that only high-quality, safe and effective medicines and medical devices are placed on the market in Switzerland.

[3] See chapter 12.

The interviews and visits aimed at:

- Providing additional information regarding the evidence or inconsistent approaches of AAM (chapter 6).

- In describing the Swiss market and its potential of development (chapter 7), the purpose was to compare the case of Switzerland to that of Japan: Japan is not only the country with the highest proportion of older persons, but also a leading country regarding age-specific interventions. Through a review of literature (state-of-the-art), the report lists preventive interventions and reviews the evidence at two levels: a) on better and healthier ageing and b) on anti-ageing medicine.

Expert Opinion Survey Response

Out of 120 experts contacted worldwide, 2/3 responded among which 55 fully completed their questionnaire and the rest either answered very partially, could not answer or had never heard of anti-ageing medicine. In the experts who completed the questionnaire, 23% were women and 77% were men aged 45 to 73. More than half (60%) had a medical degree, whereas 40% came from different disciplines: public health, health care, nursery, health economics, psychology, or social gerontology. Among those with a medical degree, most of them were specialised in geriatrics (some in internal medicine or endocrinology) and came from different countries: Belgium, Brazil, Chile, France, Germany, Israel, Spain, Switzerland, the United States and former Yugoslavia. Most of those interviewed were not active users of AAM. Only 20% declared using such medicine and only one expert used DHEA,[4] no one consumed growth hormones.

[4] DHEA (adrenal hormone dehydroepiandrosterone) – see chapter 5.5.2.

3. From Population to Individual Ageing

Summary: Demographic data shows that population ageing is increasing. This phenomenon is due to increased longevity and life expectancy in the majority of countries in the world. People are living longer and in better health than ever before. Research demonstrates that healthy and successful ageing is not a myth but a possible reality for all, countering the prejudice according to which if you are old, you are sick and disabled. In this context, the biological theories on ageing have witnessed a reverse trend, which started a controversy between (i) the traditionalists who do not believe humans can prolong their life with or without interventions, and (ii) the protagonists of a continuous increase longevity and a disease-free life through early detection and prevention (and AAM), which is supported by the progress of life science technology. Prevention and intervention today follows 3 patterns: a) the classic model of decline with ageing, b) better and healthier ageing through prevention programmes, and c) anti-ageing medicine and long life preservation of health and peak performance with the use of new technologies (from biomolecular to surgical interventions, from dietary supplements to robotic environments).

3.1. Population Perspective

3.1.1. The Population Ageing

Never in the history of mankind have we witnessed a 'silent revolution' of such significance for all sectors of society. Population ageing, a global phenomenon, is affecting every individual, society and policies in industrialised countries and more and more in countries in transition. It is a 'revolution', because of its significance. It is 'silent', because this revolution remains nevertheless relatively unclear or not prioritised, despite the tremendous challenges it presents in terms of social cohesion and individual and family values. Today, evidence shows we live a longer life, in better conditions, and in better health than in any previous century.

Certain experts have even called this fact an 'Agequake,' or a 'New International Demographic Order'. The population growth followed by the current decline in growth rates, the fertility decline, an increased life expectancy, changes in living conditions and technologies, the increasing urbanisation, and migration are all cumulative factors of this new demographic order which affects all countries worldwide.

Data and population census reveal throughout the world the constant increase in the number and proportion of the elderly. Presently 673 million inhabitants in the world are aged 60 and above, among them 88 million are more than 80 years old. According to the United Nations 2006 Prospects (UN, 2007) the expected numbers for 2050 are of 2 billion (60 and over) and 400 million (80 and over), which means a multiplication by 3 and 4.5 respectively, of older (respectively oldest-old) populations.

Today, 21% of the European population and 17% of the Northern American population are aged 60 and above. Those figures will increase to 35% and 27% respectively by 2050. The challenge in industrialised societies is that ageing will progressively impact on every country in the world. One half of the oldest-old population (80+) currently lives in the most developed countries (among them 29% live in Europe and 13% in Northern America). During the coming decades, less developed countries will however also observe a significant demographic ageing and in 2050 the majority of the elderly (62% of the 60+) will live in Asia (Kinsella and Velkoff, 2001; UN, 2007).

Population figures for Switzerland clearly show the expected emergence of the elderly. According to the most recent demographic forecasts (SFSO, 2006), 17.6% (1.33 million) of the current population are 60–79 and 4.7% (355,000) are 80 and above. The expected percentage for 2050 are 22.5% (1,82 million) and 11.7% (942,000), which means that one out of three Swiss residents will be aged 60 and above. Until 2050 the number of people aged 60–79 will increase by 36%. The increase in the number of oldest-olds will be of 165% (compared to 6.6% for the total population (table 2).
Therefore, the observed 'silent revolution' is far from being merely demographic; it is multidimensional and global. The consequence on the development of nations is already felt by the individual, the family and at the social level in the whole world—for example, in the area of distribution and access to all the facilities which guarantee health, lodging, work, social welfare, security,

technology, etc. Policies must be updated regularly, or even newly designed, to adjust existing structures to the new population architecture and to abate or prevent social tensions due to economic and technological constraints and health care rationing.

Table 2: Age Structure in Switzerland, 2007–2050 (numbers and percentage)

	2007	2010	2020	2030	2040	2050	Trend 2007–2050
Age groups							
Population							
0–19	1,626,182	1,594,093	1,520,975	1,495,395	1,444,461	1,397,442	-14.1
20–39	2,024,032	2,024,443	2,038,877	1,931,112	1,851,223	1,828,350	-9.7
40–59	2,222,792	2,282,708	2,304,524	2,177,285	2,167,348	2,078,167	-6.5
60–79	1,332,890	1,410,085	1,679,463	1,911,777	1,909,844	1,815,032	+36.2
80+	355,355	380,963	458,952	627,318	778,106	941,729	+165.0
Total	*7,561,251*	*7,692,292*	*8,002,791*	*8,142,887*	*8,150,982*	*8,060,720*	*6.6*
Proportion							
0–19	21.5	20.7	19.0	18.4	17.7	17.3	
20–39	26.8	26.3	25.5	23.7	22.7	22.7	
40–59	29.4	29.7	28.8	26.7	26.6	25.8	
60–79	17.6	18.3	21.0	23.5	23.4	22.5	
80+	4.7	5.0	5.7	7.7	9.5	11.7	
Total	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	

Source: Swiss Federal Statistical Office SFSO, 2006

The epidemiologic (or mortality) transition does not only impact on age structure, but also on the quality of life of the elderly. Numerous studies show the regular improvement of the health status of the elderly. For instance, according to the Swiss Health Surveys, the proportion of people aged 65–79 complaining of symptoms of bad mental health decreased from 22% to 11% between 1992 and 2002. The general improvement in health also leads to an increase of the disability-free life expectancy (DFLE). *In Switzerland and according to the same surveys and mortality tables, DFLE at the age of 65 increased by more than one year between 1992 and 2002 for women, to reach 21 years.* This means that a woman of 65 years can expect to live 21 more

years without any incapacity. Among men, DFLE at the age of 65 in 2002 was 17 years, 1.5 years more than in 1992 (Guilley, 2005). Similar trends are observed when considering life expectancy in good subjective health.

Such trends mean that the elderly not only live longer, but are also in better health and have other expectations regarding leisure and ways to spend the last part of their life. Moreover, in comparison to their parents and grandparents, they also benefit from more financial resources. Recent studies demonstrate that in industrialised countries aged populations present an increasing level of income and wealth.

Contrary to what was observed some decades ago where a high level of poverty characterised older people,[1] the elderly are now in a better financial situation than young adults. Recent studies conducted in Switzerland (Moser, 2002, 2006) highlighted that the elderly declare a higher level of wealth than younger people (in the Canton of Zurich one out of four retired couples are millionaires) and that they also regularly (and sometimes rapidly) increase their wealth. Official data confirms this statement suggesting that the proportion of persons who get social benefits from the public sector is significantly lower among the elderly than among the young.

Different factors explain the new socioeconomic status of the elderly. First, the present population of retirees benefited from a period of rapid economic growth, and a large percentage was able to take advantage of this situation to accumulate savings. This phenomenon is well known for the Baby Boomers, a population born during the 1940s and 1950s characterised by a successful active life and thus well placed financially. Second, the implementation of social security systems in industrialised countries contributed to decreasing the risk of poverty among retirees. Not only are public expenses for retired persons very high (the amount of total public expenditure for retirees is approximately ten times higher than the cost of supporting families), but individual retirement plans are more and more frequent. Third, sexagenarians are the main beneficiaries of inheritance (Stutz and al., 2007), which undoubtedly increases their level of wealth. Their investments are also less risky which increases wealth (Wanner and Gabadinho, 2007).

[1] Although the subject does not only address persons of higher ages, the term ‘older people’, adopted by the UN, is used throughout this report.

In some groups however, the risk of poverty is high, in particular for those with long-term illnesses and widowers as these groups often have the lowest level of income and little wealth (Wanner and Gabadinho, 2007). But the number of elderly able to live a successful life after 65 is on the increase.

The effect of technology on globalisation has produced a society centred more on what is 'new', 'young' and 'fast', to the detriment of some traditional and common values among all generations. Healthier, wealthier, and the 'median' elderly have new expectations regarding the late part of life. The traditional model, where life was divided between youth and adulthood is progressively replaced by the current model of four stages: youth, adulthood, third age, and fourth age. Third age, also called 'a second youth', is nowadays an opportunity for new occupations and the increase of leisure activities. According to the Havighurst and Albrecht's (1953) theory of activity, retirement is replacing professional by non-professional activities. The participation in social activities is important, as a positive image of older people is a factor of integration in society. According to this theory, old age and its consequences should be fought to its very limits, and this fight is necessarily connected to the maintenance of health.

3.1.2. Decrease in Mortality Rates and Health Improvement

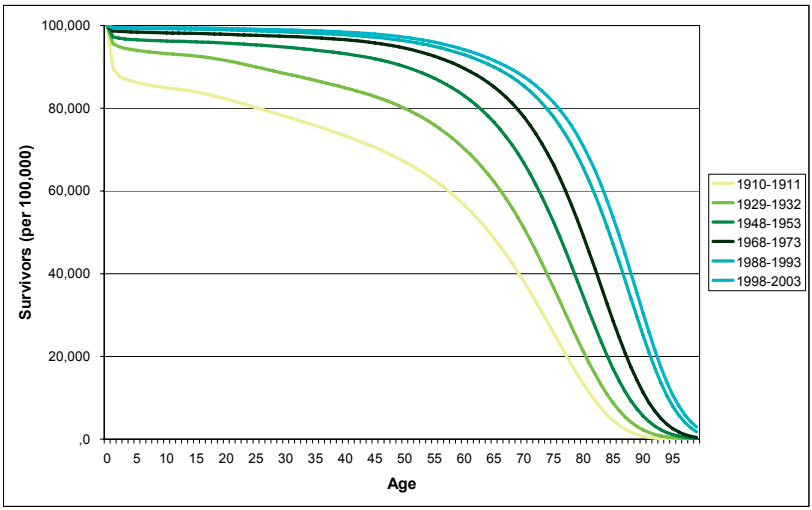
As mentioned, the decrease in mortality rates is the main factor of demographic ageing in industrialised societies. It also indicates a general improvement in health that is illustrated by the Swiss data.

Switzerland experienced a rapid increase in life expectancy towards the end of the 19th and all through the 20th century. In 1900 life expectancy at birth was of 48.5 years for females, and 45.7 years for males. Today's life expectancy is of 82.8 years (females) and 77.2 years (men), and the progression has not stopped.

Such trends lead to a rectangularisation of the survival curve as illustrated in figure 1 (Paccaud et al., 1998). With the increase of survival rates observed in young aged people, more and more people die at the same ages—between approximately 75 and 90 (figure 1). At the extreme end of this curb, everyone would die at the same age—the maximum lifespan. In this hypothetical case, the survival curve would be rectangular. The part of the figure located on the

upper right-hand side above the curves represents remaining gains in life expectancy to reach a whole equality. Differences between curves describe progress observed during the last decades.

Figure 1: The Rectangularisation of Survival Curves for Women in Switzerland 1910–1911 to 1998–2003



Source: Swiss Federal Statistical Office SFSO, 2006

The increase in life expectancy is not a worldwide phenomenon. Countries such as Romania or Russia have recently observed a decrease of life duration after the end of the communism regime. Japan showed in 2005 a curious decrease in life expectancy, which needs to be confirmed. However, let us be reminded that life expectancy is a “mean number” which can decrease through increase of younger generations or HIV-AIDS pandemic and does not exclude the existence of a high number of older persons.

Analysis of the population longevity development shows that the spectacular increase in life expectancy during the last century is linked to many factors such as the improvement of hygiene and sanitation, the progress of medicine and public health and better treatments and prevention measures. Experts generally mention three conditions required today for increasing life expectancy in the world: 1) a good health status of the population, 2) the absence of epidemics, and 3) a good socioeconomic and sanitarian context. If those conditions are

respected, people might progressively live longer, whatever their age and sex, as a result of the improvement in medical knowledge and the fight against diseases.

This does not imply that in Switzerland and more generally in Western Europe population's health status is not an important challenge. Up to now, epidemiological data suggest a general improvement of different health indicators during the last decades. However, the increase in life expectancy also results from the epidemiologic transition, meaning the transition from the 'age of pestilence and famine' to the 'age of receding pandemics', and finally to the 'age of degenerative and man-made diseases' (Omran, 1971). The latter characterised industrialised societies, where chronic disease and mental illness rise in importance in the population. Survey data however show a rapid decrease in different indicators of morbidity, after controlling age.

As the baby boom generation rapidly approaches age 65 and due to the increase in number of the oldest-old, solutions are sought to maintain health and autonomy in individuals throughout their life and ageing. Today, countries that are already hit by their ageing population are investing in cost-effective interventions and measures to enhance quality of life while reducing the anticipated rise in costs and medical care of the old age.

3.1.3. Biodemography and Longevity Medicine

According to an expert meeting of the International Longevity Centre in New York (2001), "longevity medicine expresses the intention of the field to extend life within what appear to be genetically determined limits, through control of the myriad diseases that afflict humanity, and through direct intervention in the biological processes of ageing. Longevity medicine should apply to all means that would extend healthy life, including health promotion, disease prevention, diet, exercise, cessation of tobacco use, as well as advanced medical care and new discoveries that result from basic research. It also suggests the ultimate possibility of identifying and even manipulating those genetic factors that may influence the genetically determined limits of the species." This definition yields towards the eventual development of authentic longevity-promoting interventions of documented safety and efficacy.

As the biogerontological establishment is striving to distance itself from the contemporary purveyors of anti-ageing products and services, research on measures to achieve what Gruman in 1966 termed 'prolongevity'[2] has become a mainstream activity sponsored and supported by institutes such as NIA in fields such as caloric restriction or dietary supplements (Masoro, 2001a, 2001b). Regardless of whether AAM research covers those areas, genetics or stem cells research, bioengineered solutions, Binstock (2004) summarises the anti-ageing aspirations of biogerontologists with 3 central paradigms: (i) compression of morbidity, (ii) decelerated ageing, and (iii) arresting ageing.

- *The compression of morbidity paradigm:* In this scenario first proposed by James Fries a quarter of a century ago (Fries, 1980, 1989), humans live long and vigorous lives, terminated by a sharp decline in functioning mandated by senescence, followed relatively swiftly by death. The compression of morbidity basic syllogism argues that the age of first signs of incapacities can be postponed while the lifespan itself is genetically determined, hence the period of age-related disability can be shortened. The ideal envisioned by Fries is for all of us to lead long lives free of chronic disease and disability, and then die rather quickly as we reach the limits of the human species life span because we are 'worn out' from the fundamental processes of ageing. Compressed morbidity includes the possibility of increasing average life expectancy, but not maximum life span for the human species.

- *The decelerated ageing paradigm:* In this scenario, the process of ageing is slowed down and average life expectancy and/or maximum life span is increased. In contrast to the compression of morbidity ideal, this theory argues that age-related functional disabilities cannot be eliminated but are postponed to a more advanced age. Aubrey de Grey, a University of Cambridge geneticist, and his colleagues argue that this phenomenon is already taking place in the context of greater average life expectancy; they do so by drawing on data showing that the onset of late-life frailty is occurring at later ages than previously, but the period of time for which it is experienced is not becoming shorter (de Grey et al., 2002a). Another researcher, Richard Miller, University of

[2] The prolongevity protagonists defend the idea that, following specific regimes and methods, individuals could live to extreme old age, well beyond the seemingly preordained limit.

Michigan, believes that through decelerated ageing it may be possible to "produce 90-year-old adults who are as healthy and active as today's 50-year-olds, as well as increase the mean and maximal human life span by about 40%, which is a mean age at death of about 112 years for Caucasian American or Japanese women, with an occasional winner topping out at about 140 years." (Miller, 2002:155,164)

- *The arrested ageing paradigm:* The processes of ageing in adults are reversed in order to restore lost vitality and function and rejuvenate the body/mind. Some scientists envision that reversal could be accomplished through strategies that remove the age-enhanced damages inevitably caused by basic metabolic processes and thereby attain 'indefinite postponement of ageing' or 'negligible senescence' (de Grey et al., 2002b). As the American Academy for Anti-Aging Medicine[3] (A4M) portrays it, success in achieving arrested ageing would be tantamount to bringing about, 'virtual immortality'—that is, an increase in healthy adult life span of such a great magnitude that the consequence would be the emergence of societies in which no one dies except from accidents, homicides, and suicides, or from choosing to forego or by avoiding the interventions that bestow continuing vigorous life (Klatz and Goldman, 1996, 2003).

3.2 Individual Perspective

3.2.1. Definition and General Theory of Ageing

While gerontology and geriatrics are relatively new sciences, the body of research, theories and definitions on ageing have flourished and expanded from the middle of last century. Thus, defining ageing is as complex as the subject of research itself. However, there is a general consensus in defining ageing with its paradox: the growth of experience in life versus the loss of functionality and vitality. The Webster Dictionary, for example, gives 4 different angles to the definition of ageing (see box below).

[3] See chapter 5.1.1.

Empirical studies show that ageing is not a one-dimensional concept but a multidimensional field of study occurring in at least three dimensions: chronological ageing, biological-physiological ageing and psychosocial ageing.

Definition of Ageing

1. The process of growing old or maturing
2. An artificial process for imparting the characteristics and properties of age
3. To become old is to show the effects or the characteristics of increasing age
4. To acquire a desirable quality (as mellowness or ripeness) by standing undisturbed for some time transitive senses

(Webster Dictionary, 2006)

The definition of ageing varies. One view, held by biologists, medical doctors and some psychologists is that ageing is associated with decline of most elements (Birren, 1964). Ageing is the point at which development has ceased and subsequent changes are seen as an aggregate of biological change beyond the point of optimal maturity (Buhler, 1968). On the other hand, life-span developmental psychology considers ageing in more positive terms: "the psychology of ageing, geropsychology, focuses on the behaviour of individuals involved in the processes of post-maturity development." (Kermis, 1984: 5) In this perspective, ageing is seen as a continuous development in old age as opposed to an irreversible decline.

In medicine, ageing is generally characterised by the declining ability to respond to stress, increasing homeostatic imbalance, and an increased risk of disease. Because of this, death is the inevitable consequence of ageing. Differences in maximum life span between species correspond to different 'rates of ageing'. For example, inherited differences in the rate of ageing affect a mouse elderly at 3 years and a human elderly at 90 years. These genetic differences affect a variety of physiological processes.

Despite the strong call of 'anti-ageists' redefining 'ageing as disease', most scientists are currently opposed to this view. Hayflick is one of them and states that even if it leads to death, ageing cannot be considered as a disease *per se* and stresses that four criteria clearly differentiate ageing from disease (Hayflick, 2000): (1) it occurs in every animal that reaches a fixed size in adulthood, (2) it takes place in virtually all species, (3) it occurs in all members of a species only after the age of reproductive success, and (4) occurs in animals removed from the wild and protected by humans even when that species has not experienced ageing for thousands or even millions of years. As Hayflick underlines: "More than 75% of all human deaths in developed countries now occur in those over the age of 75. If the causes of these deaths are resolved we will not become immortal but we will have revealed how death occurs in the absence of disease. What will be found is that the underlying cause of these deaths is the inexorable loss of physiological capacity in the cells of vital organs—the hallmark of ageing. If ageing research is to advance, it will not only be necessary to distinguish biogerontology from geriatric medicine, but it will also be necessary to distinguish ageing from longevity determination."

Since the last century, researchers have focused on trying to understand the mechanisms of ageing and the factors influencing morbidity and mortality. An impressive body of research is now available, from the cellular to the socio-behavioural perspective of the ageing processes. Each scientific discipline has built its own set of theories on mechanisms and processes of ageing and tried to reach a consensus on what is 'normal ageing' versus 'pathological ageing'. There is growing interest from diverse perspectives of science to search for a general theory that explains what ageing is and why and how it happens. Therefore, theories have been developed allowing researchers to handle an enormous amount of diverse observations related to this phenomenon. Empirical observations on ageing have become so abundant and complex that the 'Handbooks' or 'Encyclopaedias of Ageing' existing today have grown over the past decade from a single volume to multiple volumes: for example, a special four volume 'Encyclopaedia of ageing' is today required to cover the full extent of accumulated knowledge (Maddox, 1987, 1995; Ekert, 2002) or the 'Handbooks of Ageing', at their 6th edition now have three different handbooks distinguishing: biology, psychology, and a social science perspective on ageing (Masoro and Austad, 2006; Birren and Shaie, 2006; Binstock and George, 2006).

The scientific study of human ageing is multidisciplinary and complex. A systematic approach to understand the normal versus degenerative pathological processes of the human system is indispensable if one wants to intervene to prevent or alleviate the risk factors. Hence, theories on the biology of ageing must be included in a larger framework of psychological development and social theories on ageing. After introducing the general biological theories of ageing, it briefly describes two broader perspectives, the reliability theory and the developmental and social approach, which bring together a framework to understand ageing. Both the angles, the bigger picture and the smaller picture, are needed to comprehend the ageing phenomena.

The Future of Ageing: Ageing is not a Disease

"The failure to distinguish between ageing research (bio-gerontology) and research on age-associated diseases (geriatric medicine) has been, and still is, a source of misunderstanding. There is little evidence that this failure, with its important scientific, political and societal consequences, will soon be rectified. Thus, the present imbalance will continue, in which resources available for research on the diseases of old age far exceed those available to address the core question: why are old cells more vulnerable to disease than are young cells?

Policy-makers, properly impressed with the future demographics of the graying of all economically developed countries, are basing important policies and decisions on a flawed understanding of what constitutes ageing research and what they believe might be accomplished."

(Hayflick L., 2000: The Future of Ageing, Nature 408:267)

3.2.2. Biological Theories of Ageing

The fact that biogerontology, a relatively recent field of science, is still in need of a comprehensive database has led to speculations, contradictions and to a plethora of biological theories on ageing. An additional cause of the many theories on ageing is that manifestations of biological changes over time affect virtually all components of living systems from the molecular level to the whole organism (i.e. molecule, organelle, cell, tissue, organ, and organism). The hierarchical cause-effect of change over time thus leads to very different theories and research methods to test those theories. One of the methodological problems underlined by many theorists is that change that is more fundamental than the one observed may induce the effect that was chosen for study (for an exhaustive review and discussion see Masoro and Austad, 2006).

On the other hand, the AAM protagonists have harnessed the complexity of correlated factors' influence over time to question the universality of theories on ageing and argue for an 'open upper limit' to human life span.

No Limits to Life Span?

"Age-related changes do not occur uniformly in individuals; rather they are controlled jointly by genetic and environmental factors which further heighten the difficulty of finding a universal theory. What is universal is that we are all involved in a global-ageing phenomenon. Through theoretical gerontology and anti-ageing medicine we may eventually discover there is no limit to human life span."

(Dr. Hans Kugler, Editor of the Journal of Longevity Research,1993)[4]

As all fundamental life processes depend on genetic events, biological theories of ageing have first concentrated on genetic events. Today, most scientists agree that ageing is not a programmed process governed directly by genes. Studies in lower animals that have led to the identification of genes involved in

[4] The Journal of Longevity Research, later called "Journal of Longevity", is a monthly magazine that the Braswell company publishes, one of the biggest AAM profit-making companies in the history, pinned down by the U.S. government hearing as producing anti-ageing products with fraudulous scientific information, doing business primarily under the name GeroVita International, markets pills and potions through the mail (see GAO, 2001).

ageing have not shown a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of ageing. Those studies are more accurately interpreted as showing that certain genes impact on longevity determination because the results alter physiological capacity and occur before the ageing process begins. Age-related disorders stand out in contrast to the ordered change that occurs during genetically driven embryogenesis and development. “Humans, from conception to adulthood, are virtually identical in respect to the stages and timing of biological development but from about thirty on, age changes make humans much more heterogeneous.” (Hayflick, 2000) As nonagenarians and centenarians also display a different pattern of healthy survivor typology, it is suggested that genes might play a ‘re-emerging role’ in extreme longevity (Perls, 1995).

From Hayflick’s point of view (1996, 1998), ageing is a stochastic process that occurs after reproductive maturation and results from the diminishing energy available to maintain molecular fidelity. This disorder has multiple aetiologies including damage by reactive oxygen species. Longevity determination, on the other hand, is not a random process. Energy is better spent on guaranteeing reproductive success than it is for increasing individual longevity. Many species die soon after their reproductive role is fulfilled. Consequently, age-weakened individuals living beyond reproductive success have diminishing value for the survival of a species and will be culled by natural selection. Longevity is governed by the excess physiological capacity reached at the time of sexual maturation that, through natural selection, was achieved to better guarantee survival. For this reason, the question, ‘Why do we live as long as we do?’ might be more appropriate than, ‘Why do we age?’ According to evolution theories, ageing is usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age. Such a trait, which impairs survival and fertility, is clearly negative for the individual. An explanation for evolution of ageing suggested that senescence is programmed to limit population size and accelerate the turnover of species (Kirkwood, 2005; Kirkwood and Austad, 2000). Moreover, primary system failures result from prior changes in interrelated repair, regulatory, homeostatic and adaptive mechanisms.

From a biological perspective, some scientists have come to the following basic question on the origin of ageing: how can we explain the ageing of a system built out of ‘non-ageing’ elements or structures? This question leads us to start

thinking about the possible systemic nature of ageing and see if ageing is a property of the system as a whole evolving through human species with increasing longevity. While non-ageing is possible at the micro-level, the meso and macro-ageing is a fact and cannot be discarded in explanations of ageing. Three of the major evolutionary theories which have tried to answer this systemic perspective on ageing and longevity will be presented here:

- *Mutation Accumulation Theory:* From the evolutionary perspective, ageing is an inevitable result of the declining forces of natural selection with age. For example a mutant gene that kills young children will be strongly selected to disappear in the next generation, whereas a lethal mutation that affects people over the age of 80 will experience no selection because people with this mutation will have already passed it on through their reproductive age. Over successive generations, late-acting deleterious mutations will accumulate leading to an increase in mortality rates late in life.

- *Antagonistic Peiotropy Theory:* Late-acting deleterious genes may even be favoured by selection and be actively accumulated in populations if they have beneficial effects early in life.

- *Epigenetic Theory* (see box on page 28): Epigenetics is seen as affecting profoundly our understanding of inheritance. Epigenetics adds a whole new layer to genes beyond the DNA. It proposes a control system of 'switches' that turn genes on or off—and suggests that experiences people live, like nutrition, stress, violence or trauma, but also healthy lifestyles (and potentially AAM), can control these switches and cause heritable effects in humans. During 2007, more than 2,500 articles, numerous scientific meetings and a new journal were devoted to the subject of epigenetics, one of the most exciting contemporary biological theory portrayed by the popular press as a ‘revolutionary new science’. The basic revolution in the paradigm of epigenetic theory is that genes hold a memory of the living conditions affecting our direct ancestors through an epigenetic (or mutational) change of state (Bird, 2007). The Epigenetic Theory and its growing field of research is bringing a paradigm shift in scientific thinking but also holds social and moral implications: individuals adopting healthy/non healthy lifestyles or experiences do not just live a life affecting them solely, but they can

play a crucial role in the health of their children and grandchildren for generations to come.

Those three evolutionary mechanisms are not mutually exclusive and may operate at the same time. The main difference is that in the mutation accumulation theory, genes holding negative effects in old age accumulate passively from one generation to the next, whereas in the other theories, these genes are actively kept in the gene pool by selection or activated/deactivated throughout the lineage by a system of 'turning on/off gene switches'. The relative contribution of each evolutionary mechanism to longevity has not yet been determined and is today the main focus of research in evolutionary theory. Although the role of transgenerational transmission of behaviour has been addressed by a few authors (Thornstam, 1989; Stuckelberger, 2002, 2005), the transgenerational transmission of 'active vs. non active' genes is recent (see box on page 28). The transgenerational perspective calls for a new dimension of individual and 'lineage responsibility' in lifestyles, physical and mental health, social interaction and environment. In this context, the question of AAM interventions and of modifying the natural human constitution through biotechnology and bioengineering widens the spectrum of long term risk vs. benefit analysis with new ethical implications.

Epigenetic Theory and Applications

"The Ghost in Your Genes": Scientists believe your genes are shaped in part by your ancestors' life experiences (BBC Science Programme excerpt)[5]

The air they breathed, the food they ate, even the things they saw can directly affect you, decades later, despite your never experiencing these things yourself; equally what you do in your lifetime could in turn affect your grandchildren. Through mice embryo manipulation, Prof. Wolf Reik, at the Babraham Institute in Cambridge studied this hidden ghost world and managed to set off 'switches' that turn genes on or off, and discovered that these switches themselves can be inherited. This means that the 'memory of a life event' could be passed through generations. A simple environmental effect could switch genes on or off—and this change could be inherited. Consequently, genes and the environment are not mutually exclusive but are inextricably intertwined, one affecting the other. The idea that inheritance is not just about which genes you inherit but whether these are switched on or off is a whole new frontier in biology. It raises questions with

[5] See http://www.bbc.co.uk/sn/tvradio/programmes/horizon/ghostgenes.shtml

profound implications, and it implies research on the kind of environmental effects that can influence these switches.

Examples of growing evidence in humans:

- *Environmental factors passed down to future generations:* researchers in Sweden have shown that a famine at critical times in the lives of the grandparents can affect the life expectancy of the grandchildren. This is the first evidence that an environmental effect can be inherited in humans (Pembrey, 2002).

- *In-vitro fertilisation impact:* studies show that babies conceived by IVF have a three- to four-fold increased chance of developing the Beckwith-Wiedemann Syndrome, a rare disorder linked to abnormal gene expression (e.g. Maher et al., 2003; AGART, 2005[6]).

- *Impact of stress and tragic events on the embryo:* Pregnant women present during the September 11 World Trade Centre collapse have passed on markers of Post Traumatic Stress Disorder (PTSD) to their unborn babies through transgenerational transmission. The findings strengthen the evidence for in-utero or early-life risk factors for the later development of adult mental or physical disorders (Yehuda et al., 2005).

3.2.3. New Paradigm: Reliability Theory of Ageing and Longevity

One of the most prominent and revolutionary theory today has been developed by two Russian researchers, Gavrilov and Gavrilova, through the reliability theory of ageing and longevity (2001, 2004, 2006).

Ageing occurs in animals and humans but can also be observed in technical devices or structure (such as cars or houses), which do not reproduce themselves in a sexual way and are therefore not subject to evolution through natural selection. Therefore, Gavrilov and Gavrilova argue that, "the evolutionary explanation of ageing based on the idea of declining force of natural selection with age is not applicable to ageing technical devices, and that there may be another more general explanation of ageing." (2006: 5)

[6] AGART – Advisory Group on Assisted Reproductive Technologies, Ministry of Health, New Zealand.

Reliability Theory: the Analogy of Clocks Functioning as a New Clock vs. Failing Clocks

The reliability theory views ageing as a phenomenon of *increasing risk of failure with the passage of time (age)*. If the risk of failure is not increasing with age ("the old is as good as new"), then there is no ageing in terms of reliability theory even if the calendar age of a system is increasing. For example, clocks that count time perfectly are not ageing according to reliability theory—although they have a perfect 'biomarker' for their continuous age changes: a displayed time and date. Thus, the regular and progressive changes over time *per se* do not constitute ageing unless they produce some deleterious outcome (failures). In terms of reliability theory, the dating problem of determining the system's *age* (time elapsed since system creation) is different from the *performance assessment problem* of a system's ageing (old becoming not as good as new). Perfect clocks having an ideal marker of their increasing age (time readings) are not ageing, but progressively failing clocks are ageing (although their 'biomarkers' of age on the clock's face may stop at a 'forever young' date).

(Gavrilov and Gavrilova, 2006:5–6)

Reliability theory was first developed to describe the failure and ageing of complex electronic equipment. The theory itself stems from of a general theory based on mathematics and a systems approach (Barlow and Proschan, 1975; Barlow et al., 1965).

Many advantages can be found in the reliability theory:

(1) It provides a common scientific language (general framework) for scientists working in different areas of ageing research.

(2) It helps understand and define more clearly what ageing is.

(3) It is useful for generating and testing specific predictions as well as deeper analysis of collected data.

(4) It helps researchers develop intuition and understanding of the main principles of the ageing process through simple mathematical models featured in the reality of the material world.

(5) It gets scientists away from an 'absolute' negative paradigm to a relativity approach mixing observations on ageing and non-ageing aspects.

System failure is central to the reliability theory. Failure is defined as the event when a required function is terminated (Rausand and Hoyland, 2003), it occurs when the system deviates from its function. Failures are often classified in two groups: (1) the degradation failures in humans correspond to the onset of different functional impairments and diseases, whereas (2) catastrophic or fatal failures correspond to death.

According to the reliability theory, ageing is not just growing old, but a degradation leading to system failure, which in turn leads to adverse health outcome or mortality. From this point of view, ageing cannot be seen through the 'failure' lens of disease—ageing is disease and decline, but is not linked to age *per se*. Ageing without diseases is inconceivable. Healthy ageing is an oxymoron like 'healthy disease' or 'healthy death' and the authors suggest that instead of speaking of 'successful ageing' or 'ageing well', more appropriate terms would be 'delayed ageing', 'postponed ageing', 'slow ageing', 'arrested ageing', 'negligible ageing' and even 'ageing reversal'. From this point of view, it could be said that reliability theory is very close to an anti-ageing perspective. On one hand ageing is seen as a period of high risk in 'maturation of diseases', but on the other hand, not every disease is related to ageing.

Anti-ageing interventions may also be outcome-specific and limited to postponing some specific adverse health outcomes. Ageing is likely to be a convenient term for many different processes leading to various types of degradation failures. Thus, each of these processes and their triggers deserves to be studied and prevented or modified (see box below).

Reliability Theory and Anti-Ageing Interventions: the Example of Hip Replacement

One may wonder whether hip replacement surgery would qualify as an 'anti-ageing intervention'. The answer to this question is not as simple as the question itself. It is conceivable that hip replacement therapy may prevent some patients from physical inactivity, stress, depression, loss of appetite, malnutrition, and drug overuses. The result may be that further progression of some diseases and disabilities could indeed slow down compared to patients who did not receive this treatment. In this case we can say that hip replacement therapy helps to oppose ageing for some specific types of degradation failures in a particular group of patients (very limited anti-ageing effect). It is true, however that the term anti-ageing intervention is usually associated with hopes for something far more radical, such as ageing reversal in the future, applicable to all people.

(Gavrilov and Gavrilova, 2006:7)

This new theory gives significance to beneficial health-promoting interventions, which are often neglected or not even given credit for delaying the process of ageing. Contrary to the pessimistic view of considering pathological manifestations of ageing as normal, this theory says that there may be no specific underlying elementary ageing process itself but only preventable failures of parts or the whole. Therefore, small and partial success of each particular intervention is a success in opposing the failures of the system. Thus, "the efforts to understand the routes and the early stages of age-related degenerative disease should not be discarded as irrelevant to understanding 'true' biological ageing; on the contrary, the attempts to build an intellectual firewall between biogerontological research on clinical medicine are counter-productive" (Gavrilov and Gavrilova, 2006).

3.2.4. Theoretical Rationale Behind AAM

Biogerontologists and evolutionary theorists have throughout the years developed a vast array of theories that remain to be further developed or refuted depending on empirical findings. While some have been discarded, they can still be considered partly relevant for the debate on anti-ageing medicine.

The following theories (see list below) are the most often cited by the anti-ageing medicine movement as their basic framework for testing new hypothesis and conducting research. Those theories each represent a research area and show how much must still be done to prove which theory is wrong and should be abandoned or finds sufficient evidence to be taken into account in the big 'puzzle' of understanding the ageing process and the regenerative/decline mechanisms.

Biological Theories on Ageing: the Basis of AAM

- *'Wear and Tear' Theory* (introduced by August Weismann in 1882, 1891, 1892): the ability of normal somatic cells to replicate and function is limited, therefore ageing occurs because the body and the cells are damaged by overuse and abuse; a worn out tissue cannot renew itself forever. In the evolutionary context, according to Weisman, ageing occurs to benefit the species by removing less fit animals from an environment where limited space and other resources should be conserved for the young.
- *Hayflick Limit Theory:* on the basis of Weisman theory, two cell biologists, Leonard Hayflick and Paul Moorehead in 1961 demonstrated the limited ability for normal human/animal cells to replicate and function which, they argued, is a fundamental reason why the lives of individual animals and humans are finite. Hayflick theorised that the ageing process was controlled by a biological clock contained within each living cell.
- *Neuroendocrine Theory* (introduced by Vladimir Dilman, 1981, 1986, 1992): based also on Weisman 'wear and tear' theory, but with focus on the neuroendocrine system.
- *Free Radical Theory* (introduced by Rebeca Gerschman and her colleagues in 1954, then developed by Denham Harman, 1956): normal oxygen consumption inevitably results in the production of oxygen free radicals, which in turn damage important biological molecules. Over the last half-century the free radical theory has developed into the *oxidative stress theory of ageing* following the observation that the damaging reactive oxygen species (ROS) are not all free radicals and by also taking into account the organism's antioxidant defences. This theory proposes oxidative stress and the consequent damage is also responsible for processes such as the clustering of degenerative diseases in the terminal part of the life.

The oxidative stress theory is currently the most popular mechanistic theory of ageing and there is much evidence, mainly indirect, to support it (Sohal and Weindruch, 1996).

- *Waste Product Accumulation Theory* (Henry Hirsch, 1978): in the course of their life spans, cells produce more waste than they can properly eliminate and when accumulated it can interfere with normal function and trigger degeneration processes. As the body ages, its cells are less able to dispose of accumulated waste and they slowly die. This is similar to the *Limited Number of Cell Divisions Theory:* the number of cell divisions is directly affected by the accumulations of the cell's waste products. The more wastes we are accumulating over time the faster cells degenerate.
- *Delayed Expression of Deleterious Genes:* Peter Medawar (1957) argued that the presence of deleterious genes in a species could be kept still by a selection process that would postpone their manifestations if it were not possible to eliminate them. Deleterious genes could pile up in the post-reproductive period when their expression would do less harm to the specie.
- *Errors and Repairs Theory* (Peter Medawar, 1952; Leslie Orgel, 1963): the natural repair processes are incapable of making perfect repairs. As a result, errors creep into the molecules that compose our body causing metabolic failure, resulting in age changes and finally death.
- *Redundant DNA Theory:* like the error-and-repairs theory the redundant-DNA theory blames errors accumulating in genes for age changes. But as these errors accumulate this theory also blames reserve genetic sequences of identical DNA that take over until the system is worn out (no designated author of the theory).
- *Programme Theory of Ageing:* unlike for stochastically based theories as error accumulation, the adherents to this theory postulate a programmed and purposeful sequence of events written into the genome. This would lead to planned age changes in the same way as development sequences are orderly expressed (no designated author).
- *Cross-Linkage Theory:* introduced by Johan Bjorksten in 1942 (1968), this theory states that with age, some proteins, including collagen, become increasingly cross-linked and may obstruct the passage of nutrients and wastes into and out of cells. In addition,

excess sugar molecules in the blood can react with proteins causing cross-links and the formation of harmful free radicals.

- *Rate of Living Theory and Lifetime Energy Potential:* the German physiologist Max Rubner (1908) noted that the lifespan of five mammalian species (guinea pigs, cats, dogs, cows and horses) increased with body size, and he calculated that the lifetime mass-specific metabolic rate was similar for all five species. The fundamental argument is that Rubner's 'lifetime energy potential' (lifetime aerobic metabolism) is relatively constant for animals of different life span.
- *Entropy Theory or Order to Disorder Theory:* in terms of modern physics, a genetic programme should succumb to the 2nd law of thermodynamics, which states that a closed system tends towards a state of equilibrium or of maximum entropy in which nothing more happens. Ordered systems tend to move to greater disorder. Therefore the well-organised genetic programme, by increasing entropy, becomes disordered, producing those changes recognised as ageing. Disorder occurs in molecules in turn causing other molecules to produce errors and these chaotic changes in our cells, tissues and organs is what causes ageing (no designated author).
- *Theory of Cell Damage, Balance and Transportation:* adherents of this current point out that cell survival requires detoxification and an appropriate balance of nutrients, water, electrons, antioxidants, electrolytes, hormones, and acid-base, among others. All the above require good transportation in order to reach the cell. This means open capillaries and lymphatic's imbalance will cause cell suffering and finally will bring cell degeneration or death (no designated author).
- *Immune (Autoimmune) System Theory* (Roy Walford, 1969, 1974; Walford et al., 1978): the immune system is the most important line of defence against foreign substances. With age, the immune system's ability to produce antibodies necessary to fight disease in adequate numbers and of the proper sort declines—as does its ability to distinguish between antibodies and proteins. The ageing immune system may mistakenly produce antibodies that work against itself.
- *Caloric Restriction Theory:* caloric restriction or energy restriction is a theory proposed by Roy Walford (1983, 1986), who has developed a high-nutrient low-calorie diet demonstrating that 'under-nutrition

without malnutrition' can dramatically retard the functional, if not the chronological ageing process. An individual on this programme would lose weight gradually until a point of metabolic efficiency was reached for maximum health and life span. Walford stresses the importance of not only the high-low diet but also moderate vitamin and mineral supplements coupled with regular exercise.

- *Stochastic Theory of Stem Cell Renewal* (Matthew Bjerknes, 1986): As we age, the native stem cell reserves we are born with diminish, along with our ability to repair and regenerate tissues. Our bodies increasingly accumulate damaged and dysfunctional cells, leading to age-related changes in the skin, organs, sex glands, immune system, blood-forming system, muscles and other systems. Stem cells are known as the 'Master' cells and have the ability to duplicate endlessly. Furthermore, when targeted at an organ and tissue, they have the ability to become cells of that tissue. Therefore a recent theory emerged from many scientists, the Stem Cell Renewal Theory, which proposes that stem cells are naturally released by the bone marrow and travel via the bloodstream toward tissues to promote the body's natural process of renewal.
- *Telomere Theory of Ageing,* discovered by scientists at Geron Corporation in Menlo Park, California (Alexey Olovnikov, 1996): This theory was born from the surge of technological breakthroughs in genetics and genetic engineering. Telomeres are sequences of nucleic acids extending from the ends of chromosomes, and act to maintain the integrity of our chromosomes. With each cell division, the telomere shortens and, after a specific number of cell divisions, it stops dividing, leading to cellular dysfunction and cell death (apoptosis). Over time, this cumulative cell senescence (death) contributes to the ageing process. In 1989, an enzyme, the telomerase, was discovered which could prevent the shortening of the telomere, and repairs the damage and maintains the telomere's length and stability, prolonging the ability of the cell to continue dividing. Telomerase is considered potentially to hold the key to unlocking the mystery of ageing by its ability to prolong cell division and slow down or even reverse the ageing process. Scientists discovered the key element in rebuilding our disappearing telomeres in the 'immortalising' enzyme telomerase, an enzyme found only in germ cells and cancer cells (Drassinower and Fabian, 2005).

3.2.5. Theories on Ageing: Socio-Medical Perspectives

Research has proven that the process of ageing is not identical for all. More recent researches conducted with large samples of population followed up for many years have demonstrated that the decline during the course of life is not inevitable: certain physical and psychic functions may not only be regained but regenerated and functions reversed (e.g. MacArthur Study: Rowe and Kahn, 1997). Those findings have revolutionised the way scientists were thinking about the ageing process until this century: whereas everything so far had inclined us to believe in the irreversibility of the condition, a new picture of hope in a 'healthy ageing standard' is since possible to envision. On the other hand, medical and technological progresses in surgical operations and therapeutic interventions may restore lost functions of certain organs (e.g. orthopaedic prostheses, operations on eyes, pacemakers, etc.), modifying the idea of the unavoidable.

The question of the difference between normal ageing and pathological ageing has also fuelled many debates. While one was accustomed to 'pathologising' ageing by considering it as an 'illness' and even a 'handicap', today the facts prove that with adapted behaviours during the life course one can remain self-sufficient for a long period of time and in good physical and psychic health. The specialists have stated long ago that the processes of intrinsic ageing were above all genetic, the alterations of physical and cognitive functions being thus inherent to a 'normal ageing'. The elaboration of the model of 'successful ageing' by a team of American researchers (Rowe and Kahn, 1997, 1998) has thwarted this trend, backed up by proof and made some headway in the evolution of gerontology and geriatrics. Today, the process of ageing is seen as based on a model with several possibilities according to the accumulation of positive risk factors during life.

Successful ageing goes beyond the absence of illness and the maintaining of functional capabilities. Their combination with an active involvement in life represents the concept of successful or optimal ageing: successful ageing involves dimensions such as lifestyle, nutrition, developmental psychology, and also genetics. The various patterns invite us to be very cautious about generalising a model of ageing marked by the inevitable decline of the human being and to distinguish properly the fields and dimensions of ageing without prejudice and age discrimination.

a. Myths and Facts on Ageing

One of the obstacles hindering the improvement of the quality of ageing and the recognition of the value of older persons in society is unquestionably the 'ageist' attitude (a term which characterises discrimination and prejudice against the elderly in the same sense as racist, sexist), which is still highly prevalent in most sectors of society. Numerous stereotypes persist concerning the definition of ageing and old age, both in the general population and among professionals.

Table 3: Contrasting Stereotypes and Scientific Realities on Ageing

Fiction: the Stereotype *- known as 'ageism' -*	**Scientific facts**
"To be old is to be sick, dependant and senile."	The majority of older persons age in good mental and physical health. Statistics show that the majority of retirees, even at 80 years old, are independent and live at home. In the developed world, the younger generations of retirees have benefited from the improvement of public health and social security measures, higher education, and better economic situation.
"The secret of ageing is well in the genes."	Our ageing process can be modulated at each stage of our lives. Twin studies have shown that with age the influence of genes diminishes and other factors such as life experience and culture cumulate and have more weight.
"The elderly can't learn anything."	At all ages, one can learn, develop and expand knowledge and skills. Concepts such as continuous education or Life-long Learning (LLL) are now well established; Universities of 3rd Age (and 4th Age) as well as 'Senior web networks' have flourished around the world.

"Older persons can't direct their lives, are not productive and are a burden to society."	Today, the generations of retirees are healthy, active and creative; most of them can and want to participate in society, they have a role and responsibility in the way they use their full civil citizenship. For example, the American Association of Retired People counts today more than 30 millions members and stands as one of the strongest political lobby in the United States.
'No cash return' when investing in the eldery	The older persons do contribute to the economy of the nation and the family through informal work and volunteering, through financial transfers to younger generations but also as consumers.

Source: Stuckelberger, 2006, modified from Rowe and Kahn, 1997

These biased opinions come from the strictly rooted references of the chronological and administrative age of retirement as a mark of old age, but also from the projection of preconceived ideas and images of old age passed on from the last century to this day, whereas life's realities have changed. Scientific facts prove that people do not grow old in the same way or in the same context as their grandparents or past generations.

As table 3 shows, the myths on the passive, ill and declining elderly persons unable to learn or take part in society, are quite outdated and quelled by the realities of scientific findings: the majority of people age well, are in good health and can play a key part in society. Despite this positive tendency, the process of ageing and decline can still lead to a series of chronic conditions and incapacities that reduce communication and mobility of the individual, thus lowering considerably his or her quality of life and increasing the health care expenditure. Evidence from economic studies of health care have proved that it is the last year of life is the most costly, in particular the last 3 months of life, independently of the age of the person (Zweifel et al., 1996). This of course is linked to a period of high prevalence of co-morbidity and incapacities, which is most often included in the data of the general population thus inducing a bias in measuring the older population health status—hence, it should be considered as a specific period *per se.*

b. The Concept of Successful Ageing

Although the concept of successful ageing dates back several decades, it is only since the last two decades that it has taken a prominent place as a guiding theme in gerontological research and health policies. In 1987, John Rowe and Robert Kahn took up the concept of 'Successful ageing' more systematically by opposing pathological norms of ageing with usual and successful ageing (Rowe and Kahn, 1987). They underlined the fact that research in ageing had emphasised average age-related losses and neglected the substantial heterogeneity of older persons with a substantive group ageing well. According to those authors, the effects of the decline process with ageing had been exaggerated, and the modifying effects of diet, exercise, personal habits, and psychosocial factors underestimated. Since then, those authors have developed categories within 'normal ageing' with a distinction between 'usual ageing', in which extrinsic factors heighten the effects of ageing alone, and 'successful ageing', in which extrinsic factors play a neutral or positive role (see graphic).

Defining Successful Ageing:
a Multi-Disciplinary Perspective

There is no single well-accepted definition or model of successful ageing that has stood the test of time:

- "Adding life to the years" and "getting satisfaction from life"
  Havighurst (1961)
- "Multiple physiological and psychosocial variables …"
  Rowe and Kahn (1987)
- "Elderly define successful ageing in term of strategies for coping"
  Fisher (1992)
- "Refers to reaching one's potential and arriving at a level of physical, social, and psychological well-being in old age that is pleasing to both self and others."
  Gibson (1995)
- "A comprehensive definition of successful ageing would combine survival (longevity), health (lack of disability), and life satisfaction (happiness)."
  Palmore, Encyclopaedia of Ageing (1995)

The concept has brought researchers in gerontology and geriatrics to shift their perspective in designing questions and in research methodology directions. In 1990, Paul and Margareth Baltes, published "Successful Ageing: Perspectives from the Behavioural Sciences" and contributed considerably to advancing new models of ageing. They underlined the contradiction posed between 'ageing' (giving a picture of loss, decline and approaching death) and 'success' (connoting gains, winning the game and positive balance sheet). The association of ageing with success, seemed intellectually and emotionally a paradox, further criticised for setting a notion of competition and a capitalist view of constant gain and denial of loss. It is interesting to note that the statements made in 1990 could be applied today to anti-ageing medicine:

Indicators of successful ageing What are the indicators of successful ageing is a complex and often debated question. It challenges the notion of success (e.g. is living as long as possible a success?). It is widely recognised that indicators of successful ageing today must consider not merely quantitative but qualitative aspects of life, requiring a multi-criteria approach: length of life, biological health, mental health, cognitive efficacy, social competence and productivity, personal control and life satisfaction. However, no consensus has yet been achieved on the relations between those criteria and their relative importance.

The categorisation of criteria poses another dilemma: the validity of subjective versus objective criteria of successful ageing and better ageing. While social sciences and psychology use extensively social or subjective criteria measures (e.g. life satisfaction, subjective health, health beliefs, self-concept, self-esteem, sense of control, coping, etc.), medicine and fundamental science rely often exclusively on objective criteria (e.g. metabolic measures, sensory tests, physical or cognitive performance, functional assessment, etc.). Humans are able to 'successfully' adapt their subjective assessments to objective conditions. Successful ageing or better ageing has become a worldwide aim, but it is still not clear which indicators characterise a person as successfully ageing.

Successful Ageing vs. 'Natural' Ageing?
Debate of the 1990s

"The association of ageing with success might indicate that the apparent contradiction is intended to provoke a probing analysis of the nature of old age as it exists today. We are asked not only to reflect upon but also participate in the creation of ageing, instead of passively experiencing it as a given reality that is 'natural' only for the reason it exists. In this sense, the concept of successful ageing suggests a vigorous examination of what might in principle be possible. Moreover, a critical but constructive analysis of the concept may indeed serve to articulate the idea that forms and vehicles of 'success' in old age may be different from those in earlier phases of life."

(Baltes and Baltes, 1990:4)

c. Ageism and Anti-Ageism: Roots for Anti-ageing Interventions

Today, theories on successful ageing from the social sciences and from the biomedical arena start overlapping consolidating the necessity to conduct multidisciplinary research in the field of ageing. Until the 1980s, successful ageing was defined in terms of 'length of life'. Researches studied micro- and macro-level factors associated with the extraordinarily long lives, from ants to drosophila, from mice to human centenarians. Others did laboratory experiments exploring the possibilities of lengthening the human life span by carefully controlling factors such as dietary intake and biomolecular changes. More recently, considerable attention has been given to investigating ways to delay the onset of disability, thereby lengthening the number of years of 'active life expectancy' and confirming the theory of compression of morbidity (Fries & Crapo, 1981; American Federation for Aging Research and the Alliance for Aging Research, 1995). This trend demonstrates the realisation among biomedical researchers that quality of life is as important as quantity of life, or is at least a necessary part of successful ageing.

The revolutionary AAM movement—focusing on erasing the external signs of ageing and slowing down the process of ageing—strives to draw together innovative solutions from all fields, from biomolecular to smart environment to quality of living. The anti-ageist counter the traditional images of ageing held by younger persons, the public in general and older persons themselves, which

have been shown too often to hold negative stereotypes and age discrimination (Höpflinger und Stuckelberger, 1999). Older people are categorised as "senile, rigid in thought and manner, old-fashioned in matters of morality and skills" (Butler, 1995).

The consequences of ageism are largely underestimated. One can for example hypothesise that the growing 'anti-ageing' movement is simply an 'anti-ageist' movement. The fact is that today one can observe new behaviours leading to combat every external sign of ageing potentially damaging and discriminating. This strive to counter ageism reflects in an increasing demand by the public for products and interventions to erase the signs of ageing and possible discrimination. The adoption in 2000 by the European Union of directives and legislation[7] to fight age-discrimination as well as the ongoing vacuum of bioethical guidelines on old age and end-of-life reflect clearly the fact that society and policy have long been impregnated with the post-world war image of aging (Stuckelberger et al., 2007; Stuckelberger, 2006, in press).

d. Successful and Better Ageing on the Political Agenda

Terms such as 'healthy ageing', 'successful ageing', and 'active ageing' have become increasingly common in research protocols and policy documents. Many governments have today adopted better, healthier, more active or successful ageing policies. Core active ageing practices include life-long learning, working longer, retiring later and more gradually, being active after retirement and engaging in capacity-enhancing and health-sustaining activities. Such practices aim to raise the average quality of individual lives and at the same time, at the societal level, contribute to larger growth, lesser dependency burdens, and substantial cost savings in pensions and health. They, therefore, represent 'win-win strategies for people of all ages' (EC, 2002).

[7] Currently, the European Union (EU) member States are working on implementing EU directives in the field of equal treatment and discrimination, including age discrimination, due to the reinforcement of fundamental rights and non-discrimination in the EU with the proclamation of the Charter of Fundamental Rights at the Nice European Council on 7 December 2000. Article 21 of the charter prohibits discrimination on any ground such as sex, race, colour, ethnic or social origin, genetic features, language, religion or belief, political or any other opinion, membership of a national minority, property, birth, disability, age or sexual orientation and also discrimination on the grounds of nationality.
See: http://ec.europa.eu/justice_home/fsj/rights/discrimination/printer/fsj_rights_discrim_en.htm

'Better Ageing' includes all dimensions of healthy ageing and active ageing, but goes beyond the traditional concept of health by taking into account new scientific determinants of quality of life in old age, human rights and equity, as well as environmental and technological factors. The European Commission (EC) has highlighted the importance of this issue in its EU Public Health Programme, and in 2004 the EC approved support for the three-year multinational project 'Healthy Ageing'[8], which aims at reviewing the literature on evidence-based health promotion, synthesising current practices and policies for older people's health across Europe and making findings accessible to practitioners and policymakers.

The need to improve and increase the exchange of knowledge on healthy ageing is a challenge for industrialised countries. Prevention for older people is a developing new policy area in Europe, which has closely followed the establishment of national health strategies such as the EU Policy on "Healthy Ageing in Europe: a Keystone for a Sustainable Europe" (2007)[9], the EU report "Healthy Ageing: a Challenge for Europe" (2006)[10] or the WHO "Age-friendly Cities" initiative (2007).[11]

In a report published in 2006, Switzerland has been pinpointed by the OECD and WHO for not investing more in prevention and health promotion while it has one of the most costly health systems in the world. The OECD-WHO report stresses that while Switzerland has the highest health-care costs in the world after the United States, other industrialised nations achieve comparable or even better results on smaller budgets. They also note that just 2.2% of the Swiss health budget goes towards prevention and promotion work compared with an average of 2.7% in other OECD countries.[12]

[8] See: http://www.healthyageing.nu/templates/Page.aspx?id=1054

[9] "Healthy ageing, a keystone for a Sustainable Europe", EU Health Policy in the Context of Demographic Change (January 2007): http://ec.europa.eu/health/ph_information/indicators/docs/healthy_ageing_en.pdf

[10] http://www.healthyageing.nu/templates/Page.aspx?id=1258

[11] http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf

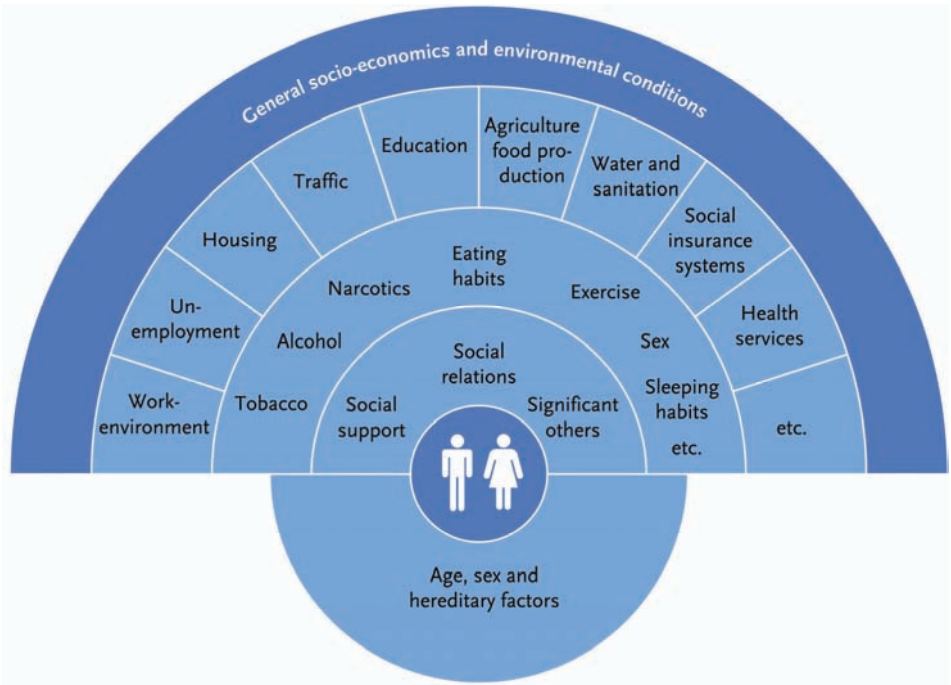
[12] For full text of OECD report on Switzerland, see report: http://www.oecd.org/document/27/0,2340,en_2649_201185_37561819_1_1_1_1,00.html German press release: http://www.oecd.org/document/23/0,3343,en_2649_201185_37567831_1_1_1_1,00.html French press release: http://www.oecd.org/document/47/0,3343,en_2649_201185_37562223_1_1_1_1,00.html

Prevention for older people is effective, affordable, and fulfils moral and ethical responsibilities. During the last decades, a wide-ranging body of evidence has been amassed to show that prevention strategies do delay or prevent disease, disability and dependency, and so reduce the need for health and social care support in later life. Results, however, take time to prove since it is a longer-term process than, say, a coronary bypass operation. And while both actions aim to reduce the impact of coronary heart disease, the money invested in prevention has a long term profit for health care expenditure by postponing first occurrence and decreasing the incidence of the disease. Hence, prevention is a motivation both for policymakers and the population; it holds an underestimated positive impact on many people of all ages for invaluable periods of time. It is a low-risk, high-value expenditure.

Much can be done, after the age of 65, by society and by older people themselves, to enable every ageing citizen to remain active and in good health; nonetheless, health in later life obviously reflects the experiences and choices made earlier in life. These measures do not necessarily entail costly public policy interventions, but rather require an effort to ensure consistent messages and actions across sectors of society. Research shows that the key factors influencing health are predominantly outside the health sector and cover a wide range of other policies.

A recent study, “Healthy Ageing in Europe” (Dahlgren and Whitehead, 1991), shows that the factors, which influence health are numerous and interrelated (figure 2). The first layer includes the close family relations such as children’s relations with adults, the social network and support from friends and neighbours and the community. The next layer includes the lifestyle factors such as eating habits, physical activity, sleeping habits, alcohol, and tobacco use. The more peripherical circle includes social, environmental and institutional conditions in which people live and work. These are determined by housing, education, social services, traffic, work environment, health care and others. In addition, there are major structural determinants, including environmental and socio-economic strategies.

Figure 2: Health Determinants



Sources: Dahlgren and Whitehead, 1991, and the EU Healthy Ageing Report, 2006

3.3. Two Views: Better Ageing and Anti-Ageing

'Better ageing' and 'anti-ageing' both strive to improve the quality of life of older persons and of the ageing population. Beyond their commonalities, marked differences exist in their approach of health, prevention, treatment and interventions. Thus, the following chapters will address each subject separately:

→ ***Chapter 4*** offers a review of efficient interventions aiming at slowing down the irreversible decline associated with ageing, while avoiding diseases and loss of function ('better ageing').

→ ***Chapter 5*** will present the definition of anti-ageing medicine, the specialities and interventions it includes, and provide state-of-the art on reliable scientific evidence existing to prove what works or does not work in the anti-ageing medicine compendium and products. This will be based on the model of preventive strategies and measures to slow down, arrest, or reverse the process of ageing ('anti-ageing').

'Better ageing' includes policies and strategies to guarantee the highest level possible of health across the life span by adopting healthy and active lifestyles and decreasing risk factors through a preventive approach. According to a recent Swiss report, improving health and quality of life ('successful ageing') while decreasing health care costs requires 3 health policy measures (Monod-Zorzi et al., 2007):

i. *General prevention:* which includes the traditional lifestyles determinants and is also profitable to the old and frail elderly;

ii. *Prevention aimed at specific pathologies:* simple and relatively low-cost interventions (eye surgery of cataract, hip replacement, etc.), which can reduce short and long health care costs;

iii. *Improvement of social life:* through family, proxy or volunteer visits and care, an older person can avoid isolation or exclusion which often leads to malnutrition and immobility which in turn leads to a decrease in physical and mental health. Maintaining older persons

> at home as long as possible with mobility and independence is the best guarantee of reducing health care costs of institutionalisation.

'Anti-ageing' contrasts with 'better ageing' in its way of pushing further what it considers as the traditional medicine. The policy of anti-ageing is to be alert to new scientific and technological findings in order to apply, use and profit from it to enhance the constitution and counter the marks of ageing. It pulls together the most up-to-date findings which are proven or give hope to build a better body, mind and functionality all through life. It strives to attain the peak performance in as many areas of human life as possible to combat ageing and contribute to the quality of life. Although no one can stop the clock of time and its marks on our lives and metabolism, findings nevertheless suggest that we can intervene on different 'body parts' and 'stop' or 'return' to a former stage of the time process. That is what anti-ageing medicine claims.

When analysing the current models of the ageing process, three different ageing patterns can be identified with specific health and life style strategies regarding prevention, treatment, intervention and products. These interventions vary not only in the intensity devoted to slowing down or countering the effects of ageing but also in the modalities of the intervention as described below and in figure 3.

a) *Classic Traditional Model of Ageing* – 'Decline with Ageing': in this model, the underlying theory is that ageing goes through a steady and irreversible decline of all physiological, cognitive and functional capacities and structures. The thinking pattern is "ageing is shrinking and diminishing …". Therefore, the prevention measures offered by model A aim mainly at accompanying the body degeneration, either by preventive measures slowing down the decline with a range of classic health behaviour and risk control, or by curing when possible and otherwise caring for the incurable ailments or frailty emerging with age (e.g. typically this applies today to patients with Alzheimer's disease for whom no treatment yet exists, and whorequire comfort or palliative treatment and care).
b) *Better and Healthy Ageing Model* – 'Successful Ageing' this more recent model stems from results of studies on 'successful ageing' in the 1990s. Model B is based on the fact that healthy and better ageing up to the end of life is possible and the symptoms of physiological,

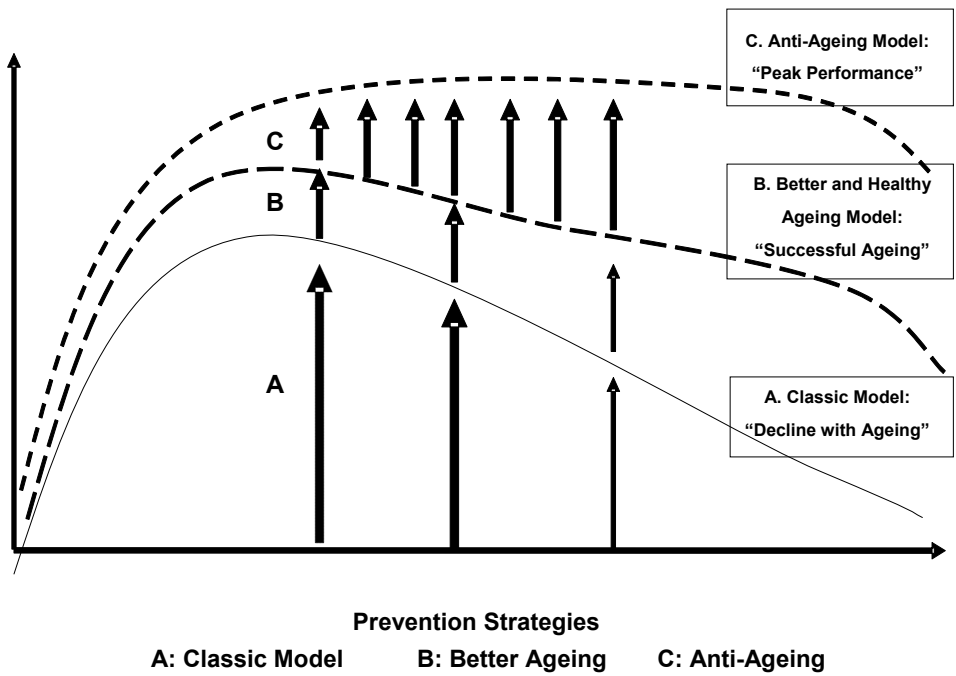
cognitive and functional decline can not only be slowed down but are, in some cases, treatable and reversible. For example osteoporosis (loss of bone mass) or sarcopenia (loss of muscle) can be reversed by targeted physical activity, nutrition, dietary supplements and/or treatment. In this perspective, ageing better by prevention related to regular screening measures of metabolic functioning is important (e.g. hypertension, cholesterol, glycaemia, cholesterolemia, osteoporosis, cardiovascular function, glaucoma). Beside the classic preventive measures, diagnostic tools also serve in regular check-up procedures at early ages, and at applying age-adapted treatments or surgery when efficient treatments exist.

c) *Anti-Ageing Model* – Peak Performances and Human Enhancement: "All you can do, do it!" – the new pattern proposed by anti-ageing protagonists revolutionises the idea and image of ageing for all generations: decline is what happens if you do not do anything, while AAM will combat any signs of decline. For the beholder of this model, maximising one's health and functional capital is a 'must', peak performance at any age is a reality if the person wants it: living longer, healthier and looking young as long as possible until death calls us (Klatz and Goldman, 2003). Therefore, AAM interventions and prevention measures (also called 'preventative ageing') are a life-long process based on a key notion of prevention: the early detection of internal and external ageing symptoms—at all ages! AAM seek to be pioneers in the use of advances and new findings in life science technology in order to respond to the individual and personalised many demands: boosting performance, enhancing 'looks' and vitality while improving all aspects of life. At the center of the philosophy of AAM lies a conception of the human body similar to a highly sophisticated engineered machinery on which technology can intervene. Thus—as in an airplane, a car or a clock—detecting at the earliest any signs or problems of deterioration in the 'body machinery' is the basis of prevention: rapid intervention to fix the problem is sought which increases the guarantee of a long lasting machinery.

While addressing A and B (Classic and Better Ageing), the model C pushes forward the screening and check-ups by using the new available technologies. A lot of out-of-the pocket investment is involved in model C as it addresses all

ages and offers a large array of efficient, non efficient and even risky products. Most health insurances will partially cover model B and even less will be covered in model C. One can easily imagine that new models of insurances with complementary conditions will appear to cover screening for modifiable risks by early detection and early prevention.

Figure 3: The Ageing Process according to 3 Prevention Models



4. Better Ageing or Anti-Ageing?

Summary: despite the rise in longevity and life expectancy, there are many different ways of ageing. To a certain extent, it is in the hands of individuals to choose the way they want to age, by maximising/minimising the known risks factors, by adopting a healthy/unhealthy lifestyle, by improving their environment. It is also in the hands of governments and public services to enable people to live a healthy and disease-free life, to facilitate mobility and interventions in those who suffer from mental and physical problems or incapacities. Through a range of policies and strategies, governments and communities can guarantee the best quality of life possible for the individual, the family and for society as a whole.

Science today demonstrates the impact of small prevention measures on health and quality of life. Better ageing as well as AAM prevention measures converge; while the latter is more 'aggressive' in its interventions, both include the following strategies:

1. **Physical activity and exercises:** consistent evidence demonstrates positive effects on mental and physical health, but also on more specific aspects of the metabolism. Significant gain in muscle and bone mass is observed even at higher ages (80 years+); AAM proposes more intensive training and performance through sports, fitness and muscle building activities and specific doping.
2. **Brain training and exercises:** mental capacities can be improved by memory training and other cognitive games or exercises; it is also recognised that physical activity has a positive impact on maintaining cognitive capacities and preventing depression. AAM studies and new punctual findings claim the regeneration of brain neurones through specific activities and 'brain food' or 'brain enhancement products'.
3. **Nutrition and dietary balance:** the access to all types of food containing diverse vitamins and nutrients for metabolic needs illustrate more than ever the importance of balancing the ingredients for healthy nutrition. Food pyramids and guidelines evolve with scientific findings and attempt to give consumers information on their natural diet. AAM is developing a new type of dietetic lifestyle by proposing artificial supplements aiming at compensating the loss of metabolic components.

4. **Long life healthy lifestyles:** a comprehensive way to lead a healthy lifestyle can be achieved through personal programmes and plans, adapted to specific situations (e.g. family), location (e.g. work) or life conditions (e.g. socio-economic status or type of work). Such plans can be designed to fit both professional and family constraints (for example, women and men vary in their daily life management depending on the family situation and children's age).
5. **Safe environment:** detecting potential ecological risk factors to intervene on modifiable aspects can enhance the quality of life. The living environment is often overlooked although reducing nuisance hold simple solutions from in-home environment to working conditions or outdoor activities. There is a particular need to address 'Health at work' and 'Health at Home' by carefully assessing any cumulative effect of daily risks, which could lead to subsequent short/long-term health problems (e.g. ergonomic, stress, air quality or building toxicity). An age-friendly city or environment, which communal and cantonal authorities can put in place, is also a pre-condition for better ageing.
6. **Multidimensional interventions through preventive services:** preventive care for older persons aiming at addressing modifiable risk factors are proven to not only reduce the functional status decline but also nursing home admission which consequently reduces health care costs. In this perspective, a multidimensional approach is needed through the application of proven successes such as preventive home visits or applying multiple health risk assessment with individualised feedback. Such strategies can take place with home visits or can be imagined on other 'living' sites.

This chapter provides an overview on 6 major areas where prevention and public health interventions have shown to be efficient in promoting individual health and maintain a high level of functionality: physical activity, mental health, nutrition, lifestyle, environment, and preventive services. It shows what commonalities and differences exist between better and healthier ageing strategies and anti-ageing strategies.

4.1. Physical Activity

> "We have an immediate, safe and reliable remedy for some of the major health risks linked to unhealthy consumption. It is free. It works for rich and poor, for men and women, for young and old.
>
> It is physical activity. At least 30 minutes each day!"
>
> (Gro Harlem Brundtland, Director General, WHO World Health Assembly, 2002)

During last decades, and with the emergence of the obesity pandemic, there is no doubt that the importance of physical activity has become the number one priority in public-health. Short and long term benefits of physical activity are recognised not only scientifically but in the eye of public opinion, whatever the age: prevention of diseases, enhancement of a healthy lifestyle, effects on a positive social life, maintenance of independence and even therapeutic effects on existing diseases. WHO stated that frequent physical activity is 'the best preventive medicine' for old age and for all ages (WHO, 2002a).

There is abundant scientific evidence that regular physical activity can bring decisive health benefits during one's life course. Even up to very a high age, physical activity is recommended and has proven to be efficient in maintaining good mental and physical functionality (Stuckelberger, in press). Regular physical activity and endurance training among older adults even leads to the same 10–30% increase in cardiovascular function as seen in young adults (ALCOA, 1999).

Despite the benefits of physical activity, the majority of adults and older persons are not physically active enough, especially among women. Furthermore, physical activity diminishes with age and the majority of older people, especially in urban settings do not engage in regular physical activity. The paradox of physical activity is that training has a considerable impact on different physiological parameters (augmenting skeletal muscle maximal oxygen consumption, muscle-fibre-type composition, capillary density, etc.), but cannot completely prevent age-related non-pathological changes in these variables (Coggan et al., 1993). Habitual activity level appears to be the critical factor in

maintaining the structure and function of skeletal muscle, and indirectly the quality of life and independent living at old age.

There is no doubt that physical activity increases endurance, flexibility and a range of motion, and balance control (Chandler and Hadley, 1996). Following the results of their 20 year follow-up study, Westerterp and Meijer (2001) stress that "losing a portion of one's physiological reserves with advancing age might be due to 'disuse and de-conditioning' and can, thus, be reversed with training". Contrarily to the belief of last century, physical activity today is even considered in specific chronic diseases as therapeutic and improving the health condition (e.g. hypertension, diabetes), more research is needed to find the precise dosage of efforts or training for the precise effects on specific conditions.

When addressing the process of healthy ageing, two perspectives on physical activity can be envisaged:

- *Better and Healthier Ageing:* physical exercise and training delays the age-induced impairment of personal mobility and maintaines physical and mental capacity. This view is based on a minimalist norm of exercise that could well reflect a cohort and cultural-historical effect.

- *Anti-Ageing Medicine*: an increase in physiological reserves of muscles is considered as countering physiological decline. Hence, physical exercise counters and reverses the 'natural' decline provoked by the cumulative absence of 'required physiological activation'. For AAM, every person has the potential to reach his/her 'long life peak performance' which is to be carefully designed with a training programme and adapted supplements compensating metabolic deficiency in order to attain a given performance.

4.1.1. Specific Interventions

The American College of Sports Medicine recommends strength or resistance training as an important component of an overall fitness programme. This is particularly important for retired or older persons who have lived passively with a 'natural' loss of muscle mass or have become 'frail'. *Progressive resistance training* is a specific training which, through a regular increase in muscle resistance, progressively generates force.

Data examining young and middle-aged endurance-trained men demonstrated that excess body fat and maximal aerobic capacity are not related to age, but rather to the total number of hours per week spent exercising (Meredith et al., 1987). Even among sedentary individuals, energy spent in daily activities explains more than 75% of the variability in body fat among young and older men (Roberts et al., 1992). Aerobic exercise has long been an important recommendation for the prevention and treatment of many of the chronic diseases typically associated with old age. These include hypertension, heart disease and osteoporosis. Regularly performed aerobic exercise increases VO_2 max (the maximum capacity to take in and use oxygen during exercise) and insulin action. However, cross-sectional data from Klitgaard et al. indicate that older endurance athletes (runners and swimmers) display fat-free mass and muscle strength similar to that seen in sedentary aged-matched controls which suggests that endurance exercise alone may not prevent sarcopenia (Laurent-Winter et al., 1990; Klitgaard et al., 1990).

Recommendations for Different Types of Training

Aerobic exercise: older persons should build up to at least 30 minutes of aerobic exercise—for example walking, swimming, water exercises and cycling (stationary or not)—on most, if not all, days.

Strength training: regular strength training (2 to 3 days a week), in a fitness centre or at home, is recommended in order to maintain bone and muscle strength.

Effective policy actions should provide opportunities for affordable, accessible and attractive physical activity for older people, particularly designed to encourage older people who are least likely to take exercise. Health education should be promoted among other people. It is also the local responsibility to ensure that outdoor environments are safe and pleasant for older people to take exercise.

The increased calorie requirements resulting from strength training may be a way for older persons to improve their overall nutritional intake when the calories chosen are nutrient-dense foods. It is particularly important to increase the intake of calcium.

4.1.2. The Anti-Ageing Approach of Physical Activities

Anti-ageing medicine will push efforts at all ages with no limitation but personal will and adaptation, with exercise preparation recommendations such as drinking water to avoid dehydration, carefully choosing the suitable exercises, and preventing accidents or body failures by paying attention to warning signs. The anti-ageing view is to conduct a medical screening and check-up before engaging with a professional trainer chosen for his empowering qualities and 'non-ageist' attitude. Too often older persons get stuck into low-aerobic activities such as walking, thereby ignoring other vital areas. The founders of anti-ageing medicine promote the idea that "no matter what your age or current condition, it is likely that your body can reach new limits of performance" (Klatz and Goldman, 1996), but they advise obtaining a medical clearance, especially for individuals with pre-existing cardiovascular disease or problems.

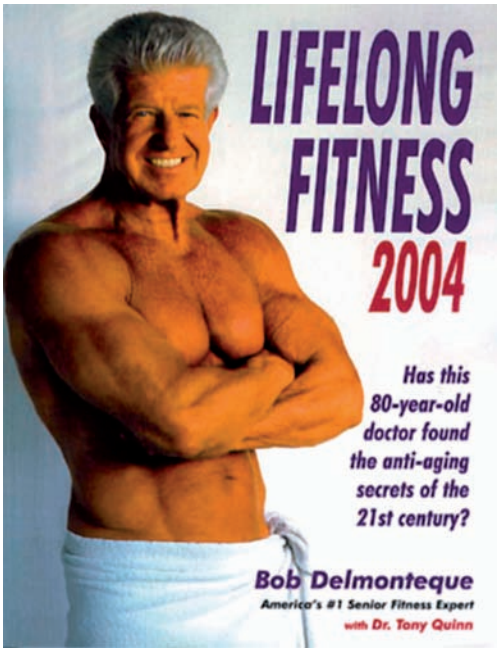
Currently, one observes a substantial lack of research and evidence on the upper limits of training intensity and duration on all measured physical activities. Ethically, research cannot take place without a hypothetical risk for the subject to suffer adverse consequences of too much exercise, but there is an opposite dilemma of not conducting research which could benefit a much larger constituency. Therefore, anti-ageing medicine takes motivating 'idols' of high training at a higher age. In their book, "Stopping the Clock: Dramatic Breakthroughs in Anti-Ageing and Age Reversal Techniques", Klatz and Goldman (1996) devote 2 chapters to physical training, one on 'training the Immortals' with classic recommendations, and the other on 'the Immortals: Successful Athletes over 60'. The latter chapter describes exceptional athletes or peak performances at higher ages which play role models, such as:

- Johnny Kelley finishing the 60th Boston Marathon at 83 years old;
- Ada Thomas starting jogging at 65, and first marathon at 69 years old, still running and playing tennis at 72;
- Ivor Welch starting athletic activity for the first time at 83, at 88 ran five marathons, and at 90 two half marathons;
- Ruth Rothfarb and Ida Mintz, both over 80, ran Boston Marathon in a little over five hours in 1991.

Defying the Physical Limits of Ageing:
Bob Delmonteque, a Successful Athlete at 85 years old

Bob Delmonteque, a Californian born at the beginning of the 1920s, is one of the most successful and known aged athletes. At 85 years of age, Delmonteque declares to run marathons, cycles 120 miles, and bench presses over 250 pounds (see www.bobdelmonteque.com). Observing that his body was starting to go downhill he decided, at the age of 65, to defy ageing.

He is the author of a best seller and is well introduced at the star system. As a fitness consultant, Dr Delmonteque has trained Hollywood legends like John Wayne, Errol Flynn, Marilyn Monroe, Clark Gable, and contemporary stars like Matt Dillon. He not only recommends regular physical activity in his approach, but also is a user of different AAM products (prostate-friendly products, collagen, and a "youth cocktail" he personally created). The youth cocktail ingredients include 60 kinds of components with amount per serving representing up to 3,000% of recommended daily value. This cocktail is on sales on the web.



4.2. Improving Mental Health

Mental health is a resource that enables us to grow and learn and experience life as enjoyable and fulfilling all through life. The World Health Organisation defines mental health as "a state of well-being in which the individual realises his or her own abilities, can cope with the normal stresses of life work productively and fruitfully, and is able to make a contribution to his or her community" (WHO. 1948).[1]

Although mental disorders are one of the main burdens of morbidity in the world, in Switzerland, policies on mental health are still largely insufficient not only for treatment but for preventing conditions leading to mental disorders (Stuckelberger, 2002).

In Switzerland, since 2002, the preparation of a federal mental health policy plan has been under way and despite many efforts among the different health systems in place at cantonal level, the architecture of an effective and efficient mental health programme and policy is still lacking. The motion of Prof. Félix Gutzwiller in March 2007[2] confirms the persistent vacuum in mental health policies—it was rejected by the Swiss Federal Government in June 2007 because it was claimed that there is no legal framework to implement such an initiative. It shows that mental health issues are still neglected, disregarded, and un-addressed at all ages but specially in old age. Many risks are modifiable and thus interventions can be efficient if implemented early enough. The aetiology of mental disorders shows a complex list of interactions between diverse factors, at the metabolic level, at the individual level (e.g. life events, death and grief, loss of status, subjective depreciation), at the social level (e.g. exclusion, discrimination, etc), or at the environmental level (e.g. stress, constraints).

While the classic interventions for mental problems, besides drugs, act on the social networks and/or use psychotherapy, a newer intervention, also claimed by anti-ageing medicine, is, for example, to restore a metabolic imbalance by nutrients supplements. Today it is recognised that mental disorders can be caused by exogenous chemical and toxic factors or by a metabolic deficiency

[1] See http://www.who.int/mediacentre/factsheets/fs220/en

[2] See document 7.3249 – Motion in German: "Psychische Gesundheit der Bevölkerung. Nachhaltige Massnahmen": http://search.parlament.ch/cv-geschaefte?gesch_id=20073249 In French: "Santé mentale de la population. Mesures durables" : http://search.parlament.ch/f/homepage/cv-geschaefte.htm?gesch_id=20073249

which for some can be restored successfully, but for others can lead to higher risks or secondary effects. In this area of intervention the protagonists of anti-ageing medicine are disputed strongly for administering vitamins, minerals, and hormones with yet little or no evidence (see chapter 5).

4.2.1. Efficient Interventions to Prevent Mental Illness or Reduce Social Isolation and Depression

Systematic reviews have assessed the effectiveness of interventions promoting mental health and targeting social isolation in older people (Tilford et al., 1997; Cattan and White, 1998). There is some support for encouraging exercise for older people in groups, both in residential and community settings, in order to promote mental health. Social isolation interventions targeted at groups such as women, or life events such as bereavement in old age were more likely to be successful (Cattan and White, 1998), and mental prevention interventions for the bereaved, and for carers were likely to be valuable (Tilford et al., 1997).

Depression is often considered to be a major health issue for all population groups. However, there is a little focus on prevention, reduction and non-drug treatment for depression in the literature, particularly for older people. According to the literature, relaxation is suspected to have a greater impact than supportive treatments, psycho-educational interventions, activity promotion and cognitive training, especially among older people (Pinquart and Sorensen, 2001). Control-enhancing interventions and cognitive behaviour therapy had an above-average impact on self-reported measures of psychological well-being (found also by Bizzini and Favre, 1997, 1998), as compared with reminiscence, miscellaneous therapies, supportive interventions, psycho-educational interventions, activity promotion and cognitive training. Psychosocial and psychotherapeutic individual interventions were associated with significantly greater improvements in self-reported psychological well-being compared with group interventions. Interventions including individual and family counselling, support groups, education and skills training can be effective in reducing psychological distress and improving caregivers' own coping skills and relationship with the person they are caring for (Brodaty et al., 2003).

Nutrients and micronutrients can also affect cognitive function, mood, and behaviour in older persons in several ways. However, the elderly are often unable to maintain a varied enough diet in order to obtain an appropriate amount of the necessary micronutrients.

In the past 5 years, accumulating evidence concerning brain plasticity in adult life and neuronal regeneration has shown the existence of angiogenesis, synaptogenesis, and neurogenesis (Fillit et al., 2002; Churchill et al., 2002). These findings do reverse the scientific belief that humans had a definite number of neurons which were decreasing irreversibly with time. The prospect of the new paradigm of brain regeneration opens a vast array of possibilities for future interventions, not only to slow down the degeneration process, but also to prevent it and maybe even reverse it. Prototype vaccines have been tested to block or slow down the progression of neurological degeneration in Alzheimer's disease in 2000 and there is hope for its final development and first clinical application around 2010 (Dubois, 2007). A review of recent longitudinal data on the possible association of different lifestyles with dementia and Alzheimer's disease (AD) systematically analysed the published longitudinal studies exploring the effect of social network, physical leisure, and non-physical activity on cognition and dementia (Fratiglioni et al., 2004): for all three lifestyle components, a beneficial effect on cognition and a protective effect against dementia has been suggested.

4.2.2. Recommendations to Improve Mental Health

a. Better Ageing Strategies

According to the 'better ageing' perspective, recommendations to improve mental health focus on:

1. making available health services and psycho-social support adapted to respond to the needs of older persons (e.g. income support, housing assistance), but also avoiding anxiety and depression caused by external factors (economic hardship for instance);

2. developing physical and mental activity among groups of older people in the community and in care institutions;

3. avoiding social isolation among specific groups (for instance the bereaved, carers or women);

4. decreasing cumulative risks of poverty, insecurity and psychological vulnerability;

5. the development of research on possible and efficient interventions.

b. Anti-Ageing Medical Strategies

On the other hand, the main objective of the anti-ageing approach is the screening and early detection of micronutrient imbalance or deficiency that might cause mental confusion, various disorders or the risk of cumulative degenerative factors (e.g. failure to repair/restore).

4.3. Nutritional Needs

Despite the rapidly increasing number and proportion of older persons in the populations, there is a scarcity of information concerning this group's specific nutritional needs according to their frailty or health condition. General dietary recommendations on what we should eat to feel well, stay fit and healthy should also exist for good ageing, as they are highly relevant to the quality of older people's subsequent health conditions.

According to the European Union's "Healthy Ageing Report" (2006),[3] old people should, for example, choose soft fats, food with good carbohydrates and large amounts of fibre, and prepare their food with as little cooking fat as possible. Other important dietary components include vitamin D and calcium, especially in the light the high prevalence of osteoporosis and hip fractures.

The Longitudinal SENECA Study Design

In 1988, the European multi-centre SENECA (Survey in Europe on Nutrition and the Elderly: a Concerted Action) study was started to determine dietary patterns and lifestyle factors affecting health and performance in Europe. At baseline 2,586 elderly persons from 19 European towns participated. Follow-up measures were carried out in 1993 (follow-up study) and 1999 (final study) in order to study changes in health status and lifestyle factors in a population that is moving from a rather healthy elderly population to a population with a deteriorated health status.

According to the study, the unhealthy lifestyle habits such as smoking, low-quality diet, and physical inactivity were each related to an increased

[3] Full report: http://www.healthyageing.nu/upload/Rome/Healthy_web.pdf

mortality risk (hazard ratios ranged from 1.2 to 2.1). In addition, inactive persons and smokers had an increased risk for a decline in health status as compared with active and non-smoking people. The net effect of a healthy lifestyle on the process of better ageing—healthy ageing is likely to go together with a compressed cumulative morbidity (Haveman-Nies et al., 2003).

Even though older people's energy requirements are lower than those of younger ones, their need for essential nutrients is just as high or sometimes even higher than for younger people. The nutrient density of food, its nutritional content in relation to its energy content, becomes increasingly important with age. Therefore, special attention needs to be paid to the balance between energy and nutrients. Among older people, higher body weight does not necessarily mean poorer health. Retained body weight in older people can be seen as an indicator of sound health (Bogers et al., 2005). The healthier 'Mediterranean diet', high in fresh fruit, vegetables, and fibre, and low in dairy fats hold true for older people (Schroll et al., 1996). Overall food consumption has been shown to fall with age in older people in many parts of Europe (Moreiras et al., 1996). The amount consumed by some older people is sufficiently small to reduce consumption of vitamins below recommended levels and cause concern about overall energy levels.

4.3.1. Factors Influencing Nutrition Over the Life Course

Nutrition at young ages bears positive and negative consequences on later life yet the present situation also plays an important role. Many factors have been identified which influence eating habits and can thus be modified in preventive interventions: physiological changes caused by ageing, consumption of medicines, disabilities, sense of taste, depression, poor teeth or fungal infection in the mouth can have negative effect on nutrition.
It was only in 2002 that the WHO published the first expert document on nutrition targeted at older persons. A year later, a technical report was published jointly with FAO (WHO/FAO, 2003) on "Diet, Nutrition and the Prevention of Chronic Diseases", taking a disease-specific approach rather than taking an ageing perspective. Both documents are based on evidence from research or reviews (see table 4) and both conclude that further research is needed to gather more information.

Table 4: Risks/Benefits of Different Factors on Health and Disease[a]

	Obesity	Type 2 diabetes	Cardio-vascular disease	Cancer	Dental disease	Osteoporosis
ENERGY AND FATS						
High intake of energy-dense foods	**R↗**					
Saturated fatty acids		PR↗	**R↗** [b]			
Trans fatty acids			**R↗**			
Dietary cholesterol			PR↗			
Myristic and palmitic acid			**R↗**			
Linoleic acid			**R↘**			
Fish and fish oils (EPA: Eicosapentaenoic acid and DHA: docosahexaenoic acid)			**R↘**			
Plant sterols and stanols			PR↘			
a-Linolenic acid			PR↘			
Oleic acid			PR↘			
Stearic acid			PR=**0**			
Nuts (unsalted)			PR↘			
CARBOHYDRATE						
High intake of Non-starch polysaccharides (dietary fibre)	**R↘**	PR↘	PR↘			
Free sugars (frequency and amount)					**R↗** [c]	
Sugar-free chewing gum					PR↘ [c]	
Starch [d]					**R=0**	
Wholegrain cereals			PR↘			
VITAMINS						
Vitamin C deficiency					**R↗** [e]	
Vitamin D					**R↘** [f]	**R↘** [g]
Vitamin E supplements			**R=0**			
Folate P			PR↘			

MINERALS						
High sodium intake			**R↗**			
Salt-preserved foods and salt				PR↗ [h]		
Potassium			**R↘**			
Calcium						**R↘** [g]
Fluoride, local					**R↘** [c]	
Fluoride, systemic					**R↘** [c]	PR=0 [g]
Fluoride, excess					**R↗** [f]	
MEAT AND FISH						
Preserved meat				PR↗ [i]		
Chinese-style salted fish				**R↗** [j]		
FRUITS (INCLUDING BERRIES) AND VEGETABLES						
Fruits (including berries) and vegetables	**R↘** [k]	PR↘ [k]	**R↘**	**PR↘** [l]		
Whole fresh fruits					PR=0 [c]	
BEVERAGES, NON-ALCOHOLIC						
Sugars-sweetened soft drinks and fruit juices	PR↗				**R↗** [m]	
Very hot (thermally) drinks (and food)				PR↗ [n]		
Unfiltered boiled coffee			PR↗			
BEVERAGES, ALCOHOLIC						
High alcohol intake			**R↗** [o]	**R↗** [p]	**R↗** [g]	
Low to moderate alcohol intake			**R↘** [q]			
OTHER FOOD-BORNE						
Aflatoxins				**R↗** [r]		
WEIGHT AND PHYSICAL ACTIVITY						
Abdominal obesity		**R↗**				
Overweight and obesity		**R↗**	**R↗**	**R↗** [s]		
Voluntary weight loss in overweight and obese people		**R↘**				
Low body weight						**R↗** [g]
Physical activity, regular	**R↘**	**R↘**	**R↘**	**R↘** [i] PR↘ [t]		**R↘** [g]

Physical inactivity/sedentary lifestyle	R↗	R↗				
DENTAL FACTORS						
Good oral hygiene/absence of plaque					R↘ [e]	
Hard cheese					PR↘	
ENVIRONNEMENTAL VARIABLES						
Home and school environments that support healthy food choices for children	PR↘					
Heavy marketing of energy dense foods, and fast-food outlets	PR↗					
Adverse socioeconomic conditions	PR↗					

Convincing scientific evidence		**Probable: growing body of evidence**	
R↗	Risk increased	PR↗	Risk increased
R↘	Risk diminished	PR↘	Risk diminished
R=0	Risk, no relationship	PR=0	Risk, no relationship

[a] Only convincing (C) and probable (P) evidence are included in this summary table.

[b] Evidence also summarised for selected specific fatty acids, see myristic and palmitic acid.

[c] For dental caries.

[d] Includes cooked and raw starch foods, such as rice, potatoes and bread. Excludes cakes, biscuits and snacks with added sugar.

[e] For periodontal disease.

[f] For enamel developmental defects.

[g] In populations with high fracture incidence only; applies to men and women more than 50–60 years old.

[h] For stomach cancer.

[i] For colorectal cancer.

[j] For nasopharyngeal cancer.

[k] Based on the contributions of fruits and vegetables to non-starch polysaccharides.

[l] For cancer of the oral cavity, oesophagus, stomach and colorectum.

[m] For dental erosion.

[n] For cancer of the oral cavity, pharynx and oesophagus.

[o] For stroke.

[p] For cancer of the oral cavity, pharynx, larynx, oesophagus, liver and breast.

[q] For coronary heart disease.

[r] For liver cancer.

[s] For cancer of the oesophagus, colorectum, breast (in postmenopausal women), endometrium and kidney.

[t] For breast cancer.

Source: adapted from WHO/FAO, 2003[4]

[4] Full report: http://whqlibdoc.who.int/trs/WHO_TRS_916.pdf, pp.147ff

4.3.2. Strategies for Healthier Nutrition

Current knowledge about the contribution of diet to health is derived almost entirely from studies of young and middle aged adults. Research is needed to establish specifically what the appropriate levels are for good functioning and disease prevention at higher ages, as well as, what constitutes 'healthy eating' for older people. However, it should be noted that older people are not a single, homogenous group. This heterogeneity is particularly true of eating patterns that vary geographically and within an age group, and also between older individuals. Diet and physical activity are today part of the WHO global strategy, and a clear resolution has been adopted by governments at the World Health Assembly in 2004 to promote both jointly (WHO, 2004).

For the purpose of helping people and nutritionists, the concept of 'Food pyramid' was first developed in the United States. But this food pyramid (figure 4a) has, since its first appearance in 1992, been rebuilt several times and is progressively adapted to scientific findings. In 1992 the U.S. Department of Agriculture officially released the Food Guide Pyramid,[5] which was intended to help the American public make dietary choices that would maintain good health and reduce the risk of chronic disease. The recommendations embodied in the pyramid soon became well-known; people should minimise their consumption of fats and oils but should also eat 6 to 11 servings a day of foods rich in complex carbohydrates such as bread, cereal, rice, pasta and so on. The food pyramid also recommended generous amounts of vegetables (including potatoes, another plentiful source of complex carbohydrates), fruit and dairy products, and at least two servings a day from the meat and beans group, which lumped together red meat with poultry, fish, nuts, legumes, and eggs. Since 1992 research has shown increasingly that the USDA pyramid is grossly flawed. In 1997, with the growing obesity pandemic in the USA, the American Dietetic Association launched a Nutrition and Health for Older Americans campaign that focused on nutrition, physical activity, and quality-of-life issues (Chernoff, 1996), targeted at the public but also at professionals.

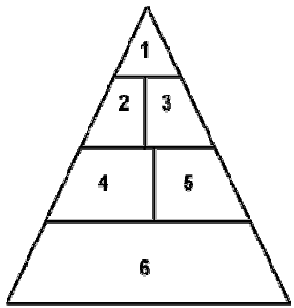
In 2005 the U.S. Department of Agriculture (figure 4a) withdrew the old Food Guide Pyramid and officially released its latest Food Guide Pyramid with a new symbol and 'interactive food guidance system', intended to help the American public make dietary choices that would maintain good health and reduce the risk of chronic disease.

[5] See U.S. Department of Agriculture Food Pyramids 1992 and 2005: http://www.mypyramid.gov

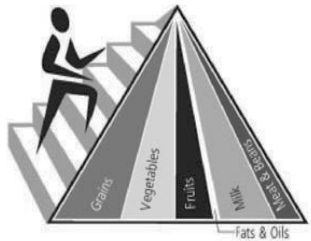
Figure 4 Food Pyramids in the USA: Government versus Academic Guidelines [21]

a. U.S. Department of Agriculture Food Pyramid

1992

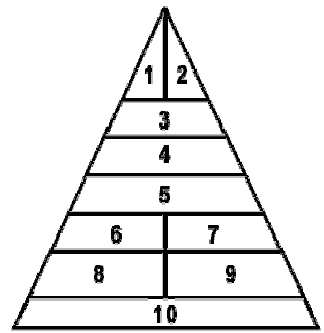


2005



1. Fats, oils and sweets USE SPARINGLY
2. Milk, yogurt and cheese 2 TO 3 SERVINGS
3. Meat, fish, poultry, eggs, nuts and dry beans 2 TO 3 SERVINGS
4. Vegetables 3 TO 5 SERVINGS
5. Fruit 2 TO 4 SERVINGS
6. Bread, cereal, rice and pasta 6 TO 11 SERVINGS FOOD

b. Harvard Healthy Eating Pyramid



1. Red meat and butter USE SPARINGLY
2. White rice, white bread, potatoes, pasta and sweets USE SPARINGLY
3. Dairy or calcium supplement 1 TO 2 SERVINGS
4. Fish, poultry and eggs 0 TO 2 SERVINGS
5. Nuts and vegetables 1 TO 3 SERVINGS
6. Vegetables IN ABUNDANCE
7. Fruit 2 TO 3 SERVINGS
8. Whole-grain foods AT MOST MEALS
9. Plant oils (olive, canola, soy, corn, sunflower, peanut and other vegetable oils) AT MOST MEALS
10. Multiple vitamins FOR MOST FOOD and Alcohol in moderation, weight control and physical exercises UNLESS CONTRAINDICATED

[21] Further explanations for a) USDA Food Pyramid see: http://www.mypyramid.gov/professionals/index.html
b) Harvard Healthy Eating Pyramid see: http://www.hsph.harvard.edu/nutritionsource/pyramids.html

The new pyramid attempts to provide individualised advice, and a web-based tutorial, taking into account factors such as a person's age, gender, and level of physical activity. It focuses on the consumption of grains, meat, beans, milk, vegetables, fruit, and oils.

A group from Harvard Medical School contested the new USDA Food Pyramid (Miller et al., 2005) and criticised its symbol 'MyPyramid' for basically reproducing the old Pyramid turned on its side. They challenged the USDA guidelines with a new 'Harvard Healthy Eating Pyramid'[6], and claimed it was based on better scientific evidence (e.g. McCullough et al., 2002). This raised the question, how to prove that their pyramid was healthier than the USDA's. To answer this question they created a new 'Healthy Eating Index' that measured how closely a person's diet followed the given recommendations. Applying this revised index to their epidemiological studies, they found that men and women who were eating in accordance with the new pyramid had a lower risk of major chronic disease. This benefit resulted almost entirely from significant reductions (up to 30% for women and 40% for men) in the risk of cardiovascular disease.

Evidence, therefore, shows that better eating is linked to better ageing. Beyond this evidence, anti-ageing medicine proposes a large array of encapsulated dietary supplements to complement the natural food ingested everyday. The objective is to compensate some of the well-documented ageing deficiencies in the body according to differential factors (e.g. vitamin D to compensate lack of sun exposure, calcium to prevent family patterns of osteoporosis, etc.).

Anti-ageing medicine harnessed this trend by proposing not only higher doses of dietary supplements of all known types, but more complex compounds with herbal or artificial molecules, either by separate product intake, or by directly introducing it in the food/beverage sold. While some of the dietary supplements are safe, because the body naturally eliminates 'overdoses' through urine (e.g. vitamin C, magnesium), others are either not proven to be safe or proven to have unsafe effects depending on the dose and on the person's metabolic condition (see chapter 5).

[6] See: http://hms.harvard.edu/public/disease/nutrition/

4.4. Lifestyles and Modifiable Risk Factors

4.4.1. The Role of Lifestyle in Ageing

Lifestyle has an increasingly important part to play in preventing, treating and preventing illness and disability, not only at a younger age, but also at an older age. There are, for instance, immediate health benefits from giving up smoking in later life (LaCroix et al., 1993; Sunyer et al., 1998) and older people should not be neglected in tobacco control policies. Recent practitioner guidance on smoking interventions for older people identifies effective interventions, many based on the 'Clear Horizons' programme designed specifically for older people (Rimer and Orleans, 1994). Alcohol may have a role in fall-related injury, cognitive impairment, and loss of mobility. Therefore, older people should not be excluded from alcohol related harm initiatives addressed to the whole community. The strategy to include the older age groups in all public health issues is today an imperative in a society with a growing ageing population.

Although it is still a largely neglected area of prevention and intervention, expert reports stress the importance of human behavioural interventions for gains in healthy life expectancy (International Longevity Center, 2001). Based on Danish and Swedish twin studies, the average set of human genes appears to be capable of getting us to at least our mid-eighties, with the majority of that time spent in good health (Perls et al., 1999). However, we are failing to take advantage of our genetic potential for longevity by engaging in practices which lead to premature onset of the degenerative diseases associated with ageing. For example, obesity in adults is a major factor driving soaring rates of chronic disease in older persons, obesity rates range from 10% to 27% in men and up to 38% in women. In the USA obesity stands at 28% for men and at 34% for women, although this can rise to 50%.[7] Our diets are overwhelmingly conducive to the development of coronary artery disease, and far too many of us still use tobacco products. If we could make major headway in eliminating unhealthy lifestyles and behaviors in industrialised countries, it should be possible to experience at least a ten-year increase in average life expectancy approximating that of Okinawans or Seventh-Day Adventists (Fraser and Shavlik, 2001). The cost savings and health-related benefits to individuals and to our society in the near future would be tremendous.

[7] International Obesity Task Force EU Platform Briefing Paper, Brussels (15 March 2005): http://ec.europa.eu/health/ph_determinants/life_style/nutrition/documents/iotf_en.pdf

Medical researchers and physicians have good evidence that lifestyle behaviour modifications can prevent or delay specific age-related diseases and disabilities, including drug treatment management, nutritional recommendations (such as increases in fibre, fruits, and vegetables), and alterations in behaviour (e.g., use of seat belts and sunscreens, adoption of regular exercise programmes, and avoidance of tobacco products). Adherence to such recommendations deserve strong endorsements, but even if everyone followed them, their net effect on longevity and the diseases of ageing would be far smaller than the effect of an intervention that slowed down the ageing process to the degree that is now routinely possible in laboratory animal models.

A classic healthy lifestyle includes a programme based on the solutions offered by research on healthy and better ageing. An anti-ageing lifestyle goes further in promoting programmes and plans designed to use all possible means to diminish the signs of ageing and reduced known factors (e.g. stress, sedentarity, malnutrition). These programmes include interventions to counter the adverse effects of ageing at 3 levels:

i) ***internally*** at the metabolic and physiological level (e.g. boosting the immune system, the DNA repair, and the cleansing of blood and vessels);

ii) ***externally***, either at the physical level (e.g. aesthetic surgery, replacement of used organs) or mental level (memory training, brain food, etc.);

iii) ***at the socio-environmental level*** (diet, physical activity, wellness to combat stress).

Websites have developed with different offers: extended plan for an anti-ageing lifestyle (e.g. www.anti-ageing-guide.com), selling ‘forever young’ products (e.g. www.foreveryoungvitamins.com) or both (e.g. www.bodyandfitness.com). Consumers are offered to ‘self-design‘ their own anti-ageing life plan based on the offers of these sites with a large list of interventions and products but no supervision or quality control. These sites go from using scientific evidence with no comprehensive view to basic information or false information, leading the person into a non-informed-based decision with potential high risk.

Included in lifestyle programmes for seniors, pharmacological interventions and supplements are often as important, for some specific chronic diseases. The literature on the use and associated problems of medication is extensive, but far

less in the area of polymedication or auto-medication in the elderly and very few directives presently exist (Stuckelberger, 2001). The WHO summarised it in its "Priority Medicines for Europe and the World" publication (Willemen et al., 2004) the recent literature on the size and nature of the disease burden of a number of geriatric diseases and of drug-related problems in the elderly. In the elderly, the problem of medication and self-medication is much more acute given the intake of large number of products at higher ages (e.g. Stuckelberger, 2001). These include adverse drug reactions and the under-use or overuse of prescribed and non-prescribed medicines. The drug-related problems include many risk categorisations: misuse or incorrect prescription, non-compliance, inappropriate medication, adverse reactions of pharmakinetic interactions, use of drugs carrying risks. In others cases there may be under-use or misuse due to misunderstanding, lack of accessibility to doctors, pharmacies, difficulties in opening drug packages, label instructions too small to read or too difficult to understand or interactions with other treatments, etc.

An overview of all the therapies and products which an individual (or a patient) can take—from artificial molecules to dietary and herbal supplements—is missing. This lack of information causes a serious public health problem addressed in 2001 by the U.S. Senate. The U.S. government proceeded to a wide consultation of experts and federal agencies to assess the health hazards senior citizens face as well as the economic abuse of false products and fallacious marketing.[8] In addition to these problems, some medicines used today by older people have not been tested on this age group, nor do many dietary supplements mention all bioactive ingredients. Furthermore, women and men's metabolism is different and does not react in the same way to specific substances, especially in the case of compounds containing hormones. It is obviously necessary to test new medications on the group who will use them the most and is most at risk of secondary effects. To improve the quality of medication in older people, Hanlon et al. (2003) suggest that older people of different age groups be included in clinical trials and surveys of specific therapies. Recommendations can also be made to test medication in animal experimental studies and clinical trials with different older age groups to analyse the right dosages according to different parameters (e.g. body frailty, gender, health conditions).

[8] U.S. General Accounting Office: http://www.gao.gov/new.items/d011139t.pdf

4.4.2. Strategies for Healthier Lifestyles

It is the wish of all governments that the population adopts better and healthier lifestyles; it is a key to a nation prosperity and economic growth as well as to social peace. Health promoting behaviour not only decreases the health care costs throughout life into older ages, but more so is a strong asset for countries productivity. Thus, healthy lifestyles and ageing can only be praised and promoted. As mentioned, Switzerland has been criticised for insufficient health promotion and prevention programmes despite having one of the most expensive health care systems in the world (OECD, 2006).[8] Therefore, more funding is needed to plan and implement policies and programmes at the federal and at the cantonal levels:

i.) targeting modifiable risk factors and lifestyles;

ii.) promoting healthy physical and mental lifestyles across the life span;

iii.) enabling the environment to facilitate mobility of older persons and avoid increasing confinement at home.

On the other hand, the population's health would gain from better information on the risks of an excessive 'anti-ageing lifestyle' which can lead to physical and mental consequences (e.g. overstraining muscles, supplement overdose or hypervitaminosis, obsessive or hypochondriac behaviour, etc.).

4.5. Environment

Both indoor and outdoor activities affect the ability of young and old to stay active, participate in and contribute to the community. Environmental improvements—whether at home, at work or in the neighbourhood—have a direct effect on the quality of life of the population especially for older persons and potential caregivers. However, more research is required in this area. Older people travel less frequently than younger people in their local area as they have no need to travel in connection with work, and they spend more time either at home or doing outdoor activities. Many older people would like to be more mobile and active (Mollenkopf, 2007).

4.5.1. Age-Friendly Environment

The naturally reduced mobility of older people, together with the lack of private or public transport "clearly demonstrates that the decline in outdoor mobility in late life is not an entirely voluntary retreat from the world. Instead, it means that elderly people are more or less being compelled to cope with health impairments and adverse external circumstances" (Mollenkopf et al., 2004).
Accessible green areas and time spent outdoors have been highlighted as important determinants of good health, as shown for instance, in Sweden's new public-health policy. Older people with poor mobility and persons with disabilities are more dependent than others on having areas for recreation and recuperation close to where they live. Pleasant design of these areas is therefore of particular significance (Nyquist Brandt and Watson, 2005).
Developments in technology influence all public domains and private life—as well as how older people can cope with these developments. Older people need encouragement and time to become accustomed to the ever-changing world of technology increasing their 'social functionality'. This challenge of adjustment is often greater for the older than for the younger generation. Technology may not be accessible, affordable or acceptable to older people.

Two systematic reviews on the effects of housing on health are reported in this chapter:

- Thomson et al. (2002) systematic review focused on determining how housing improvements could improve health in the population as a whole. The authors searched the international literature, identifying nineteen studies, the earliest from 1936. The results of this review indicated that housing improvements can generally improve health, in particular mental health; but they can also have adverse effects. Housing improvements reported in studies on re-housing and restoration can also result in rent increase and can even cause some suffering such as distress; the original residents when relocated may not benefit from the improvements.

- Walters et al. (1999) systematic review demonstrates that housing can influence older people's health in a number of different ways. Its location can influence older people's access to friends and relatives, and social facilities. The design, quality, and state of repair interact with impairments to create enabling or disabling home environments. In a Swedish study the presence of stairs was the most common housing-related reason for

> a person having to move from home to long-term care. The distance to the shops, the availability of public transport, and the work required to keep a home in good order—all these affect the ability of an older person to remain active and participate in, and contribute to society. However, interventions affecting environmental factors such as housing and planning are seldom evaluated by health outcomes. Alliances between the planning and housing sectors on the one hand, and the health and social care sectors on the other, are rarely made.

Different interventions allow people to remain in their own homes despite age-related changes, and continuing to function as members of their community. These efforts are reinforced by a move in many countries to increase the extent to which health and social care is provided within the community rather than through long-term residential care.

A Japanese intervention offering unlimited benefit grants for home adaptations and improvements found that one third of responding users improved on three health outcome measures (need for help with activities of daily living, carer burden, and need for transfer to long-term residential care). Two thirds improved with at least one of these modifications, this had a stronger effect with the more expensive change or if the bath or bathroom were modified; a decreasing need in help for activities of daily living was closely associated with improvements to entrance ways (Kuroda et al., 1994) This kind of non-cash-limited open access project is a commitment that few public sector providers would enter without proof of its cost effectiveness. This evaluation does not include an estimate of costs averted for the older persons, their carers, or the providers of health and social care. Japan with its record centenarian number and rate is very concerned with adapting the country and society to its ageing population and their specific rhythm and requirement in the everyday life. Many innovative enterprises flourish: for example two architects (Shusaku Arakawa and Madeline Gins) have developed in Mitaka area the 'Reversible Destiny Loft' which is conceptualised to constantly keep older persons stimulated and alert: visual stimulation through original colours, functional stimulation through soils that are not flat but bumpy, curved or inclined, or light switches at variable levels to require efforts even in the apartment; electronic markers are placed to facilitate the arrival of robotic aid or caregivers able to find their geo-spatial monitoring (Le Monde, 2007).

In the UK, a series of lower cost interventions to maintain as well as improve and adapt older people's houses have been evaluated for health care outcomes. These initiatives, known as 'Housing Improvement Agencies', 'Care and Repair', or 'Staying Put', tend to be locally run within the voluntary or state sector, and lack

the stability of a national programme. Their availability is therefore variable across the country and not reliable for the future.

More investment in research and development could bring innovative solutions and help in making the case for mainstreaming the best cost/benefit innovations.

4.5.2. Potential for Maintaining Long Life Function Through Planning

Older people's health and well-being are affected not only by the condition of their homes, but also by the environment and infrastructure design which can serve either as a facilitator or as an obstacle to mobility. The WHO 'Age-friendly Cities' Programme, financed by the Canadian government, was launched in 2007 and calls upon local and regional authorities to improve the outside mobility of an ageing population. The publication of an 'Age-Friendly Cities Guide'[9] with a checklist for urban planners and for older citizens can be used to monitor progress being made towards more age-friendly cities (figure 5 below). For example, promoting city walking and enjoying urban green spaces, an age-friendly city has sufficient public benches that are well-situated, well-maintained and safe, as well as sufficient public toilets that are clean, with lights, secure, handicap-accessible and well-indicated. Other key features of an age-friendly city include:

- well-maintained and well-lit sidewalks;
- public buildings that are fully accessible to people with disabilities;
- city bus drivers who wait until older people are seated before starting off, and priority seating on buses;
- enough reserved parking spots for people with handicaps;
- housing integrated in the community that accommodates changing needs and abilities as people grow older;
- friendly, personalised service and information instead of automated answering services;

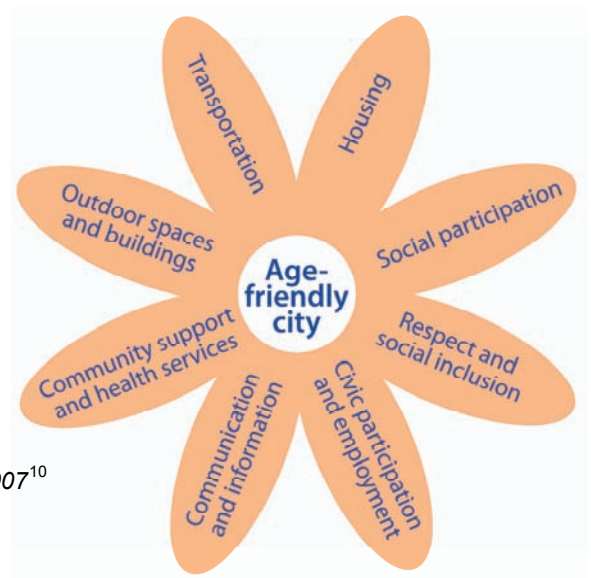
[9] Launched on 1st October 2007 in Geneva, New York and other cities in the world: http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf Geneva has already established a large programme stemming out of a community consultation and focus group organised by the City of Geneva (see http://www.seniors-geneve.ch/pdf/geneve_ville_amie_des_aines_v2.pdf)

- easy-to-read written information in plain language;
- public and commercial services and stores in neighbourhoods close to where people live, rather than concentrated outside the city;
- a civic culture that respects and includes older persons.

Furthermore, the perception of safety in the outdoor environment in the city is also a factor of mobility. Older people make decisions about the extent that they go outdoors (and therefore, maintain social contacts and remain physically active) based on perceived risks of injury and the pleasantness of the environment—matters which planners can influence.

Planners hold a responsibility in the health promotion of the population, and could be guided by policies favouring older people. The timescale of planning actions could have impacts both in the immediate short-term, and in the expected increase of older people in Europe within the coming decades.

Figure 5: WHO Age-Friendly City Topic Areas



Source: WHO 2007[10]

[10] Document available: http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf

4.5.3. Strategies

Better ageing approach recommends the following interventions:

- strategies for effective policy action on housing;
- adopt the WHO age-friendly city framework at the local level through community consultation, and eventual adaptation to rural areas;
- environment and housing quality (e.g. home insulation and safety design);
- age-designed housing for health benefits (e.g. collaboration between housing providers and health and welfare professionals);
- low cost modifications and improvements to avoid institutional care;
- standards for 'homes for life': houses which are adaptable from the outset to changing levels of disability and adjusted to each 'generation culture';
- use of new technologies in housing, facilitating independence and functionality;
- 'Design for All': European concept aiming at enhancing the quality of life of everyone and of all ages, through design, town planning, housing and everyday devices.

4.6. Multidimensional Interventions

Despite the evidence of many reports indiciating that improved health promotion and prevention might result in potential health benefits in older people, major deficits exist in preventive care or health behaviour in older persons. For example, a U.S. study uncovered major deficits in use of preventive services for older people (Pham et al., 2005). A study on health risk appraisal in three European countries, including Switzerland, reported large gaps in preventive care as well as in health behaviour among older persons (Stuck et al. 2007). There is also growing evidence on the negative impact of adverse risks on outcomes in older people. Adverse life-style risk factors, such as smoking, alcohol consumption, lack of exercise and poor nutrition have been linked to increased need for health care services; preventive interventions might not only improve health, but also reduce health care use (Leigh et al., 2005). There is convincing evidence that major adverse outcomes in older people, such as functional status decline (Stuck et al., 1999) or nursing home admission (Gaugler et al. 2007), have been linked to multiple potentially modifiable risk factors. Moreover, discrete risk factors can be successfully modified. On this basis, a multidimensional approach addressing and modifying the multiple medical, functional, psychosocial and environmental risk factors seemed to be most promising for the prevention or delay of disability in older people.

4.6.1. Preventive Home Visits

One approach for implementing multidimensional prevention and health promotion is based on preventive home visits. In general, specially trained nurses conduct initial and yearly multidimensional geriatric assessments and offer recommendations to older persons with a view to modifying relevant risk factors in the medical, functional, social or environmental area. A systematic analysis published in 2002 found that preventive home visits have an important potential to prevent or delay the onset of functional status decline (Stuck et al., 2002). However, programmes had to include several key ingredients. Such key factors associated with favourable outcomes included selection of a low-risk population, use of multidimensional assessments and multiple follow-up home visits.

These criteria are sometimes not considered practical because they require an intense and costly approach for low-risk individuals. One of the early studies meeting the criteria for a successful programme, estimated the total marginal cost of the intervention (including preventive home visits and additional physician visits) at $660 per person per year (Stuck et al., 1995). A subsequent randomised trial implementing a similar type of intervention found that the home visits increased net health care costs by approximately $400 in the first year of follow-up, but resulted in net cost savings of $1,403 per person and year in the third year (Stuck et al., 2000). Therefore, preventive home visits require a substantial initial financial investment. This does not facilitate implementation of preventive programmes for the large group of older persons at low risk, and one of the objectives of research is to find cheaper yet effective ways of implementing these types of prevention programmes. Men would benefit more particularly from preventive home care: epidemiological research has shown, while women consult more regularly physicians, men consult a doctor or a health service when it is often too late to treat the disease, which could explain their lower life expectancy (Stuckelberger et Höpflinger, 1996; Stuckelberger, 1997, 2000). Those programmes will not only be effective for better ageing but would also serve as quality control for high-risk anti-ageing interventions by offering the most up-to-date information and service to the population as well as early detection of modifiable risk factors or diseases.

4.6.2. Health Risk Appraisal of Modifiable Risks in Older Persons

Health risk appraisal (HRA)—defined as systematic collection of patient health-risks coupled with individualised feedback recommendations on reducing these risks with a view to preventing illness and disability—was first clinically applied in the U.S. in the 1980s. More recently, HRA for older persons (HRA-O) was developed for use on European populations (Stuck et al., 2007). This HRA-O approach is designed to address potentially modifiable health-risks associated with onset of disability in old age. It is based on extensive comprehensive literature reviews and a multi-step expert panel process with ongoing development work since 1992. This innovative approach includes a 32-page questionnaire covering risk-factor domains and a software programme for generating a personalised participant report and provides a summary for primary care physicians (Breslow et al. 1997).

For those elderly at low risk there is some potential benefit from multi-dimensional preventive interventions. Both, from a professional as well as from a management perspective, a multidimensional approach addressing the multiple potentially coexisting medical, functional, psychosocial and environmental problems and risks of older persons seems most promising for ensuring long-term risk-factor modification in order to respond to change over time; effective intervention programmes should include long-term follow-up. Such programmes question the need for a new health care policy vision which includes low-cost prevention programmes with high long-term cost/benefits: it is cheaper to prevent than to pay for high costs linked to care for physically, mentally and socially disabling chronic diseases, which are contemplated in Switzerland (Hopflinger und Hugentobler, 2003).

5. Anti-Ageing Medicine

Summary: Traditionally, interventions related to the ageing conditions have been the exclusive panacea of geriatric medicine. Throughout the years, the practice of geriatric medicine has gained recognition and built a strong database of evidence. In contrast, anti-ageing medicine has emerged from the geriatric medicine within a multidisciplinary group of medical practitioners and has, at first, focused on preventive medicine and early interventions to prevent ageing processes, also called 'preventative ageing', in order to offer a better and/or healthier life and ageing process. Beside pharmacological interventions and external interventions, the AAM review took into consideration three major areas: caloric restriction, cell-based therapies (stem cells) and gene therapies with predictive medicine.

Results shows a variety of level of evidence, while some interventions have been thoroughly studied in animals (e.g. caloric restriction effect on longevity and health), others have not been demonstrated in humans, although successful cases are reported in private practices. All so-called AAM interventions studied have some level of proof in humans, but can be cases in clinical practice, or applied to specific ages or in case of deficit of a metabolic compound or particular health condition (e.g. growth hormone, statins, dietary supplements). It can be noted that, in contrast to geriatric medicine, AAM is not primarily targeting the oldest-old or centenarians, but rather a wide range of ages among the healthy or non-healthy population starting at an ever earlier age. While the users are demanding AAM and visiting numerous clinics and internet sites to buy AAM products, substantive research and technologically development are still required to generalise its application. Great progress has been achieved in technological procedure to replace or improve body function at the sensori-motor level as well as in the daily rehabilitation training.

AAM is a fascinating area of research because, like an iceberg, it uncovers a large spectrum of visible novelty while it taps into the imagination of vast invisible possibilities. It illustrates well the strong technological drive in the area of innovative treatment and prevention, but also shows the difficulty of rapid transfer of findings, with its risks and abuses. Recommendations are presented after all sections and synthesised in chapter 9.

While geriatric medicine is in the hand of specialists, anti-ageing medicine has become a motto for many protagonists out of the medical boundaries. Interventions and treatments which could only be obtained with a medical prescription a few years ago are today sold freely in many countries; medical tourism and the internet offer new alternatives in crossing over national regulations and are giving consumers the possibility to become their own anti-ageing interventions managers at their own risk as no insurance so far covers such measures; furthermore, many AAM products sold freely on internet are based on false and fraudulent information as reported by the U.S. General Accounting Office (GAO, 2001).[1] This consumer-driven market is fast invading the medical and business sector to the extent where we witness a growing confusion about anti-ageing products' effects and health hazards. The questions are thus, 'what or which products will in the short/medium/long-term have beneficial effects, no effects, deleterious, or even fatal effects?' The subsequent important policy question is, 'what should we do to protect the population from an epidemic of false/detrimental products and information?' Therefore, this review aims at providing a thorough review on the scientific evidence and practices on what works or does not work. It also hopes to clarify the grey zones where political and legislative action must be undertaken to protect citizens, medical and non medical practitioners and ethical businesses from abuse, frauds and misuses of anti-ageing interventions, products and devices.[2]

5.1. The Anti-Ageing Medicine Rationale

5.1.1. Background: Definition and Mission of AAM

Anti-ageing has come as a 'new health care paradigm'; it claims offering a solution to alleviate the future health care burden and costs posed by the

[1] The U.S. General Accounting Office (2001) went through a thorough analysis of a series of dietary and supplement products labeled as 'anti-ageing' which were considered to threaten the health of consumers. Diverse testimonies were brought in front of the Special Committee on Ageing of the U.S. Senate: product companies' respondents or scientists, as well as public health experts, former affiliates of fraudulous companies, government heads of drugs, food or cosmetics. http://www.gao.gov/new.items/d011139t.pdf

[2] Scientific evidence is based on literature reviews published in peer-review journals, meta-analysis and systematic reviews (such as Cochrane library)—to avoid overloading the text with extended research description and specific references, more details on each point are available upon request.

ageing population that is more prone to chronic and degenerative diseases as well as disabilities. Going beyond 'classic prevention', anti-ageing medicine considers itself as an extension of preventive health care, pushing multiple prevention to the limits of detection and intervention. On one hand, the metabolic age-related changes, usually identified by medical doctors in classic prevention (e.g. hypertension, cholesterolemia), are taken a step further by AAM through more refined indicators for doctors, but going-further technology is transferred to the home through self-measurement devices (e.g. hypertension device, cholesterol home testing devices).[3] On the other hand, biomarkers for specific modifications are being developed and advocated by the AAM movement (e.g. levels of homocysteine[4]), which allows practitioners and the AAM market to propose, beside nutritional changes, a list of dietary and speciality supplements to compensate for the age-related decline in metabolic measures. For example, for each age-related decrease in specific hormones, a targeted speciality supplement is proposed. The interventions can take place at both levels: internal (e.g. biomolecular or pharmacological interventions) or external (e.g. surgery, resurfacing skin techniques, wellness, etc.).

In 1993, recognising that scientific research was making many discoveries to identify the mechanisms of deterioration and vulnerability to age-related diseases, Dr Ronald Klatz and Dr Robert Goldman convened a meeting of a dozen physicians, and created 'anti-ageing medicine' and proposed a new definition of ageing. In their perspective, the frailties and the physical and mental failures associated with normal ageing are caused by physiological dysfunctions that, in many cases, can be altered by appropriate medical interventions. The following definition is given.

[3] Cholesterol, Home Testing Devices: Several devices are on the market. Some measure only total cholesterol. Others measure total cholesterol and high-density lipoprotein (HDL) or 'good' cholesterol. One measures low-density lipoprotein (LDL) or 'bad' cholesterol, HDL cholesterol and triglycerides (blood fats). The American Heart Association is discussing this new trend but has not yet taken a position on cholesterol home testing devices.

[4] Homocysteine is an amino acid, elevated levels of homocysteine (Hcy) has been shown to increase the risk for several disease states. Homocysteine levels can be accurately determined from a small sample of blood which can be done in medical practice.
See http://www.homocysteine.net

Definition of anti-ageing medicine (AAM)

Anti-ageing medicine is a medical specialty founded on the application of advanced scientific and medical technologies for the early detection, prevention, treatment, and reversal of age-related dysfunction, disorders, and diseases.

(Klatz and Goldman, cited in 2003, and www.worldhealth.net)

According to their protagonists, anti-ageing medicine is an extension of preventive health care: "If you have had your cholesterol tested, taken a lipid-lowering drug, had a mammogram, or taken HRT with thyroid, testosterone, oestrogen, melatonin, or DHEA, you have experienced anti-ageing medicine. This form of medicine is based on the very early detection, prevention, and reversal of age-related disease."[5] Anti-ageing medicine is a multi-disciplinary field which includes not only advances in the fields of biochemistry, biology, and physiology, but also mind/body medicine, sports medicine, molecular genetics, and emerging medical technologies. For this reason, AAM integrates all specialities and often a transversal approach of medicine, while promoting a different outlook on ageing.

Anti-ageing medicine strives to be evidence-based for clinically sound health care: "Indeed, only those diagnostic and treatment elements which prove their validity through independent evaluations are embraced by the 'American Academy of Anti-Aging Medicine' (A4M). With early detection and appropriate intervention, most of these diseases can be prevented, cured, or have their downward course reversed" (see table 5).

The founders have clearly marked a change with the classical model of ageing and health care for healthy ageing people, and assert anti-ageing as a new true revolution: "Anti-ageing medicine is the newest clinical medical specialty, the 'optimum' of wellness and longevity, and employs extensive therapies and treatment in the preventative health care field far beyond just cholesterol testing and mammograms. A profound paradigm shift is now underway on how the medical establishment views ageing and age-related disease."[6] For this pur-

[5] http://www.worldhealth.net
[6] http://www.worldhealth.net

pose the founders created the American 'Academy of Anti-Aging Medicine' also called more largely 'A4M' in United States with branches spreading all over the world with annual conferences.

Table 5: AAM Prevention and Intervention Areas for 'Living Better—Not Ageing Better' by the AAM founders

Hormone Therapy

- Human growth hormone (The Fountain of Youth)
- Adrenal hormone (DHEA) (The Grace Factor)
- Melatonin (The Wonder Drug)
- Oestrogen and progesterone (The Female's Monitors)
- Testosterone (The Male Motor)
- Thyroid hormone (The Regulator)
- Other hormones

Mind Over Matter

- Meditation
- Progressive relaxation
- Selected awareness
- Breath control
- Exercise and physical activity
- Massage
- Think young, live young

Nutrition and Nutrients

- Vitamins, co-vitamins and co-factors
- Minerals
- Amino acids
- Additional cutting-edge anti-ageing nutrients (selected list of fatty acids, lipids and oils)

Lifestyles for Longevity

- Long-life diet: nutrition and longevity
- Detoxification basics
- Exercises for longevity
- Secrets of the 'Immortals' (stars of anti-ageing applications)
- Sleep (The Revitaliser)
- Mind over matter: anti-stress tips for anti-ageing

Skin your anti-ageing survival suit

List of more than 50 cutting-edge dermatological ingredients targeting timeless beauty

Emerging Environment Hazards affecting the Ageing Process

- Home pathogens: bedroom allergies, cleaning products and material, laundry bacteria, garden soil toxicity and pesticides
- Bacterial outdoor hazards or the 'sick house' syndrome, day care centre, sick building syndrome (office), health care settings, gym, swimming pool, hotel
- Cellular phone radiation
- Car gas

Source: Klatz and Goldman, 2003

Mission of A4M

"A4M is also dedicated to educating physicians, scientists, and members of the public on anti-ageing issues. A4M believes the disabilities associated with normal ageing are caused by physiological dysfunction, which in many cases are ameliorable *[sic]* to medical treatment, such that the human life span can be increased, and the quality of one's life improved as one grows chronologically older. A4M seeks to disseminate information concerning innovative science and research as well as treatment modalities designed to prolong the human life span. Anti-ageing medicine is based on the scientific principles of responsible medical care consistent with those of other healthcare specialties."

(www.worldhealth.net)

The A4M is the most challenging element to the established gerontological community. Not only because of the significance of the anti-ageing global market, but also because this movement claims to be "the undisputed leader in advancing anti-ageing medicine around the world" with 12,000 members and receives 1.8 million hits per month on its website (Klatz and Goldman, A4M, 2003 – www.worldhealth.net).

Although A4M is not recognised by the American Medical Association or the American Board of Medical Specialities, it has established three board certification programmes dispatching training all around the world. This academy breaks away from classic medicine markedly by its scope on

anticipating not only diseases, but more so any signs of change in screening methods and the use of an expanding array of biomarkers:

> "Prior to the creation of the American Academy of Anti-Aging Medicine (A4M), there was nobody in the area of health care that had attempted to incorporate all of these various paradigms together because medicine was focused on disease. It was focused on the treatment of disease processes and so it waited until something was broken, and usually inextricably broken, before it attempted to fix it. Whereas anti-ageing medicine tries to prevent things from breaking in the first place and tries to augment things so that they don't break, or if they do break, they break in a much slower, gradual effect. So, it is quality-of-life health care to a very large extent. For the whole of medical history, we've been focusing on 'Here's a disease, let's try and treat it after it develops' as opposed to 'Let's prevent the disease process from occurring in the first place.'"
>
> (Dr Klatz, interviewed in London, September 2006)

5.1.2. The Puzzle of Biomarkers

In medicine, a biomarker is an indicator of a particular disease state or a given state of an organism. In the past, biomarkers were primarily physiological indicators such as blood pressure or heart rate; more recently, biomarkers are becoming a synonym for molecular biomarkers. Biomarkers are still centre stage of debate among scientists on definition, area and reliability of current biomarker categories (e.g. molecular, metabolic, functional, disease-related biomarkers).

Biomarkers are at the centre of both anti-ageing medicine and prevention of disease or system failures. Technologies used in sequencing of the human genome, or the growth in the number of molecular entities entering the drug development pipeline have accelerated powerful discoveries and screening technologies. As a consequence, there is an escalating number of therapies. There is a pressing need to make safe and effective therapies and technologies available to patients. One approach is the use of precise clinical measurement tools to determine as early as possible a dysfunction or stage of a disease and measure the effects of targeted innovative interventions.

Gavrilov and Gavrilova (2006), the protagonists of the reliability theory (see chapter 3.3.2.b), illustrate a fundamental difference between two types of

biomarkers: biomarkers of age that focus on the dating problem of accurate age determination, and biomarkers of ageing which focus on the performance problem of system deterioration over time. According to the Russian authors, the regular and progressive changes over time *per se* do not constitute ageing unless they produce some deleterious outcome, e.g. failures of the system (Gavrilov and Gavrilova, 2006: 5–6). Reliability theory helps to clarify the difference between *age* (passage of time) and *ageing* (deterioration with age) concepts that are often confused in intra- and interdisciplinary debates.

According to different underlying theories on the ageing process, as seen in different sections, a biogerontologists, a geriatrician or a gerontologist will distinguish biomarkers of ageing in a very different light. Some geriatricians and psychiatrists deny the existence of any reliable biomarkers of ageing today: "It must be noted that testing the efficacy of anti-ageing remedies presents special problems because we do not have valid biomarkers of ageing: we cannot objectively measure age. We have no objective biological measurement that applies to everyone at a specific age and we have no instrument to measure age objectively in that we lack the age-measuring equivalent of a scale that gives objective weight, or a thermometer that gives objective temperature." (Butler, 2001)

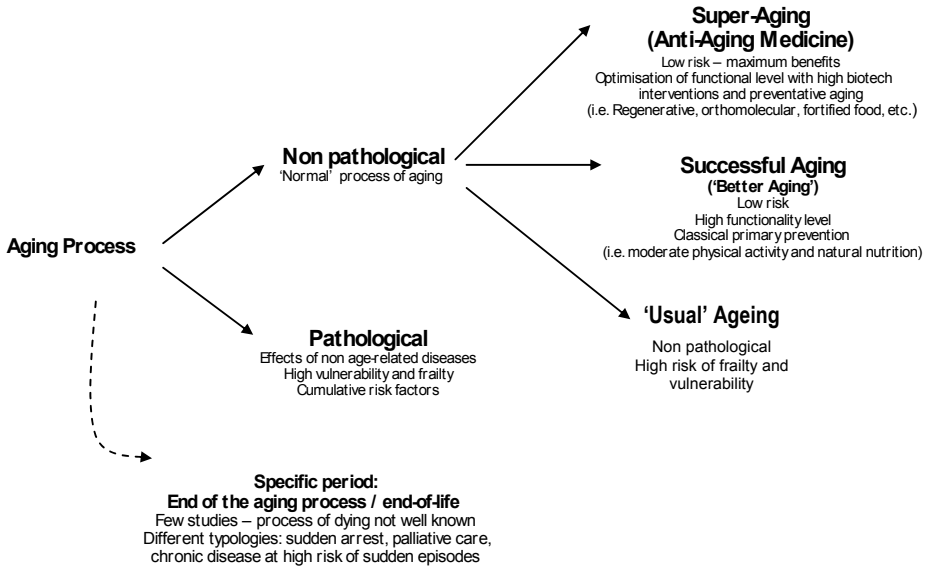
Within this framework, an 'anti-ageing' medicine could be simply defined as any intervention that delays the development of the age-dependent pathology as well as other adverse age-related changes that are not officially listed as disease.

5.1.3. Anti-Ageing Medicine: A New Option to Successful Ageing?

Science is in constant progress and search for deeper knowledge—and this is also true for ageing. Until the middle of the twentieth century doctors would tolerate medical conditions that affected older people by classifying them as incurable and adding the prefix 'senile' to the diagnosis. Some clinicians and geriatricians do repeatedly tell their patients: "Your condition is normal for your age" when treatments exist today (e.g. to combat osteoporosis and reconstruct the bone mass in a few months). It was presumed that diseases, to which older adults were particularly vulnerable, such as loss of memory, loss of audition and vision, osteoporosis and dementias were unavoidable attributes of the ageing process, and healthy ageing was somewhat of an exception.

The empirical and theoretical development on ageing clearly shows that a grey area exists between ageing and disease. Ageing *per se* puts us all at a higher risk of vulnerability to disease, functional limitations or fluctuation of our metabolic system, therefore it is ever more important to carefully monitor changes in order to intervene. For the past fifty years, research in gerontology has focused on differentiating the normative processes of ageing from the effects of debilitating diseases. The term normal ageing is still disputed today and as shown in the 'successful ageing' model, there are many pathways to better ageing or 'super-ageing', and the differentiation of a norm is between pathological ageing and non-pathological ageing (figure 6). Therefore, it is not possible to categorise as normal or abnormal, but one can try to draw a modelisation of the different pathways.

Figure 6: Modelisation and Pathways of the Ageing Process



[NB: Death, as a specific event can potentially happen at any time on the different pathways.]

Source: modified from Stuckelberger, 2006

As Binstock concludes in his analysis of anti-ageing medicine (2004): “To be sure, most if not all biogerontologists would probably quarrel with A4M’s notion that at present human life expectancy for adults can be significantly increased or prolonged (Olshansky, Hayflick and Carnes, 2002a, 2002b). But many of them believe that in the future, on the basis of further research, average life expectancy and maximum life span can be substantially extended through biomedical interventions (Miller, 2002; Lane et al., 2002; Holden, 2002).”

5.1.4. Anti-Ageing Medicine: Therapies and Products

Anti-ageing aspirations and efforts flourish today more than ever in the form of (a) research and development goals, especially in the field of biogerontology, (b) a clinical and therapeutic practice, and (c) a commercial and market oriented business. While each of these areas tests or uses the same substances and products, their aims and practices differ, as well as their legal and ethical framework. Consequently, an impressive list of compounds and products are used by consumers today, while their effect and risks are diverse in scope and not yet fully understood, thus with different degrees of safety.

For consumers, an important line can be drawn between on the one hand, prescribed drugs and treatments which are administered under medical surveillance and adapted to each case and on the other hand, products which circulate on the market as alternative therapies under the ‘anti-ageing’ label. Policy-makers and medical experts are concerned that some products have health risks or are marketed with misleading and unsubstantiated claims. Some companies promote their products to senior citizens by using ‘anti-ageing’ or ‘cure-all’ claims for which there is little or no supporting scientific evidence of safety or efficacy. In addition, some of these products may cause physical or economic harm: consumers waste money on products and alternative regimens with little or no therapeutic value, while avoiding needed conventional medical treatment.

In the scientific community, despite the reluctant attitude of many geriatricians and other medical practitioners, anti-ageing interventions are taken seriously by researchers in biogerontology and by governments themselves. After years of research on the mechanisms of ageing diseases and treatment, the U.S. National Institute of Ageing (NIA) regards anti-ageing interventions sufficiently promising to make an investment in monitoring such interventions in a multi-site pre-clinical study design to test the efficacy of interventions on life extension

(Warner et al., 2000). Four interventions are currently being tested under NIA funding: aspirin and ibuprofen derivative (both anti-inflammatory agents), hydroxyl PBN (a possible antioxidant), and nordihydroguairetic acid (a resveratrol-like compound). Ten other compounds are currently being evaluated in a second wave of tests (Binstock et al., 2006).

On the other hand, the business community has long understood the fascination of the consumers for the anti-ageing and 'eternal youth' promises. From science to business, a long path of evidence, regulation and risk management for the population is to be clarified.

Conclusion: In light of these concerns, we review the evidence of the main—and more promising—interventions labelled as anti-ageing medicine. We cannot pretend to be exhaustive as the number of interventions is increasing every day especially in the case of external interventions (chapter 5.6), where we will limit our approach to present some case-studies.

5.2. Caloric Restriction and the CR-Mimetics/Pill

Background: Caloric restriction (CR), also known as dietary restriction, is a reduction in caloric intake while still maintaining a sufficient intake of vitamins and other essential nutrients. CR-mimetics, also known as the 'anti-ageing pill' is a molecule under the form of an oral pharmaceutical, aiming at mimicking the effects of CR.

Scientific evidence: Hundreds of studies going back to the 1930s have shown that a regimen of 20–60% reduction in calories leads to a substantial increase in both average life expectancy and maximum life span in a variety of species, but especially in rodents (e.g. Weindruch and Walford, 1988). CR also lowers mortality rates and slows many of the physiological problems associated with ageing. It is estimated that caloric restriction extends life expectancy by 30–40% in experimental animals by delaying the occurrence of age-dependent diseases (Butler et al., 2002). At the cellular level, CR has been found to modulate several fundamental processes intimately involved in ageing such as retarding the age-related decline in certain DNA repair capacities or reduce an

accumulation of damage to proteins, lipids, and DNA during ageing. Masoro (2002) suggests that CR is promising: it enhances the ability to resist infections and reduces inflammation. Concomitantly, it delays the occurrence of a wide range of age-dependent diseases and disabilities such as cancers, immune senescence, cognitive decline, loss of muscle strength, and cataracts.

Challenge: Despite 70 years of research, the mechanisms of action are still unknown, but significant advances are being made into understanding the molecular and physiologic aetiology. On the other hand, application to humans remains unclear. In 2001, the Journal of Gerontology published a special issue on the effects of CR on humans. The overview stresses that there has been little research to explore the implications of these findings for the development of interventions that affect human age-related changes and diseases. One idea for transferring research from animals to humans would be further testing in prospective observational studies and on the hypothesis that voluntary weight loss does not increase (and may decrease) the risk of chronic disease or death. This would require the development of valid instruments to assess involuntary/voluntary weight loss. However, it would be difficult to develop such instruments and to avoid selection bias related to which individuals lose weight. Another unresolved issue is whether weight change may have different effects on morbidity and/or mortality depending on when the weight change occurs.

Promising intervention: Research on a small molecule in the form of oral pharmaceuticals (CR-mimetics) is currently developed and may elicit the effects of dietary CR without the need for continual restriction of food intake—as experiments and modern dietary practice seems unlikely to suit many individuals. Some CR-mimetics (e.g. oral hypoglycemic agents) have been studied extensively in humans as agents to treat or prevent specific diseases. In such cases there may be opportunities for human studies to examine other effects on age-related changes.

Several companies are currently working in this area including, for example, GeroTech and LifeGen in the US.

Conclusion: Research shows consistently that caloric restriction (CR) has a significant impact on longevity and health conditions in animal models: increase in average life expectancy and maximum life span, reduction of mortality rates, decrease in age-related morbidity, and related physiological changes associated with ageing. However, CR among humans without dietetic supervision is not applicable and may lead to malnourishment and anorexic behaviours.

Development and research is underway to develop an 'anti-ageing pill' reproducing the effects of CR without the need of food restriction. Scientists' comments reflect a high probability that it could work in humans.

Further research: The methodological problem of studying a life-long calorific restricted life is not negligible. People or groups with regular fasting habits, such as some ascetic lives or Muslim groups who would practice Ramadan with low-calorific diets every year, could be interesting groups to study.

Ethical issue: The 'anti-ageing pill' could bring about a society with double consumption (food and anti-food pill) and could be used in the context of obesity pandemic in an abusive way. Caution is needed when considering the societal and life-style consequences.

5.3. Cell-Based Therapies: Stem Cells

Background: Cell-based therapies are treatments in which stem cells are induced to differentiate the specific cell type required to repair damaged or destroyed cells or tissues. Stem cells are the ultimate resource for development, maintenance, regeneration, and repair in an organism. According to the U.S. National Institute of Health (NIH)[7] and the TA-SWISS Study on Human Stem Cell (Hüsing et al., 2003),[8] stem cells have the remarkable potential to develop into many different cell types in the body: Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is still alive. When a stem cell

[7] http://stemcells.nih.gov

[8] TA-SWISS study "Human Stem Cells" 2002: http://www.ta-swiss.ch/a/biot_stam/2003_44A_KF_Stammzellen_e.pdf

divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialised function, such as a muscle cell, a red blood cell, or a brain cell. The challenge does not only lie in the research in itself, but also in the religious and ethical debate on Life which surrounds the use of embryo stem cells, cord blood stem cells or adult stem cells, which has wide implications on funding or research and development, and of course its therapeutic use.

Scientific evidence: Despite current media coverage and controversies surrounding stem cells and their potential use in treatment of injuries and diseases, the existence of stem cells and clues to their importance were recognised as early as 1945 in bovine twins (Owen, 1945). Research over the years has demonstrated that stem cells exist in two different states; embryonic stem cell (ESC), present during development of an organism, and adult stem cell (ASC), present during adulthood. ESC are totipotent and can develop in all the different cell lineages while ASCs are pluripotent and can develop only in restricted stem cell lineages. ASCs can be found in mature organisms: their ability of self-renewal and differentiation helps maintain the organism throughout a lifetime of repair and replenishment. These critically important adult stem cells reside in many, if not most, organ systems and are defined by three major characteristics: (1) the life-long ability to self-renewal, (2) extensive proliferation, and (3) differentiation of progeny into multiple lineages.

Self-renewal, the quintessential property of a stem cell, enables that cell to make an exact replica of itself during cell division. The resulting daughter cells have precisely the same potential for self-renewal and multi-lineage differentiation as the parental cell, thus ensuring a continued supply of stem cells for the life span of the organism (Fuchs and Segree, 2000).

Stem cells are known today to have the ability to form many distinct cell types and even to correct organ level deficits, with even more potential when ESCs are involved (Binstock et al., 2006). The most important potential application of human stem cells is the generation of cells and tissues that could be used for cell-based therapies. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat degenerative diseases such as Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis. For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients

with chronic heart disease. The NIH points out that preliminary research in mice and other animals indicate that bone marrow stem cells, transplanted into a damaged heart, can generate heart muscle cells and successfully repopulate the heart tissue. Furthermore, the NIH recognises on the basis of other recent studies in cell culture systems that it may be possible to direct the differentiation of embryonic stem cells or adult bone marrow cells into heart muscle cells. For example, people who suffer from type I diabetes, whose cells of the pancreas that normally produce insulin are destroyed by their own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells into a cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics.

Successful cases in cell-therapy with specific diseases: Application of stem cells in tissue engineering for cardiac disease, as well as cartilage and bone re-construction, are state-of-the-art and most recently translated into clinical practice. As for other countries, in Switzerland heart failure is a major cause not only of morbidity and mortality but is affecting the quality of life and health care costs. Thus, the clinical application of stem cells is particularly relevant. The shared clinical feature of chronic heart diseases includes a degeneration of myocytes replaced by interstitial fibrosis, and new cells are required to repair damaged tissue; the different sources of cells transplanted for heart failure have been tested both in research and more recently in clinical trials, such as hematopoietic stem cells and mesenchymal stem cells from bone marrow and from adipose tissue (Pucéat, 2006). The failure or successful results of randomised control trials were related to the type of stem cell and the technique used: the MAGIC protocol study showed no effect (Kang et al., 2004), and the BOOST[9] trial observed cardiac function after acute myocardial infarction (Wollert et al., 2004; Wollert and Drexler, 2006; Drexler et al., 2006). The most recent large and first double-blind randomised TOPCARE-AMI trial designed by Prof. Zeiher's group in Germany (Schächinger et al., 2004, 2006), as well as Assmus et al. (2002, 2006) confirmed modest improvement in myocardial function, but Lunde et al. (2006) in Norway, who used mononuclear cells from bone marrow, failed to confirm such findings. Future clinical research of bone marrow stem cells remains controversial and uncertain before more is known on how to use then in routine clinical treatment (see box below).

[9] BOOST stands for Bone Marrow Transfer to enhance ST-elevation infarct regeneration.

Although stem cell therapy is still intensely debated, the concept of cell therapy has already been introduced into the clinical setting where a flurry of small, mostly uncontrolled trials indicate that stem cell therapy may be feasible in patients. In their review on the clinical applications of stem cells for the heart, Wollert and Drexler (2006) stress that the overall clinical experience suggests that stem cells have the potential to enhance myocardial perfusion and/or contractile performance in patients with acute myocardial infarction, advanced coronary artery disease, and chronic heart failure. The authors conclude that "stem cell therapy can be safely performed if the right cell type is used in the appropriate clinical setting. This field is now rapidly moving toward intermediate-size, double-blind trials to gather safer and more efficient data and refined methodology. Caution is required with carefully designed clinical trials keeping in mind that patient safety must remain the key concern."

Joint ventures and laboratories are growing at a fast pace to be at the forefront of research and application in Europe and in Switzerland. For example, researches carried out in Europe demonstrated advantages of using stem cells of embryonic origin due to the pharmacological potential in the course of major diseases such as Parkinson, Multiple Sclerosis, Diabetes, Cystic Fibrosis, etc.[10]

Two randomised trials show stem cell therapy benefits heart-attack patients, but third trial shows no gain at all

Two German trials that used injected stem cells to strengthen the heart muscle after a heart attack achieved positive results, while a small Norwegian trial showed no benefit. All three trials used stem cells derived from bone marrow. Perhaps the best results came from the largest trial carried out at the University of Frankfurt, which enlisted 204 patients, half of whom had stem cells injected three to seven days after a heart attack. Four months later, the injection fraction—a measure of the heart's ability to pump blood—had improved significantly in patients who were administered the stem cells. The injection fraction of the stem cell recipients improved by 5.5%, as compared to only 3% for those who got conventional treatment according to the report on 21 September 2006 in the New England Journal of Medicine. After a year, the stem cell recipients had a significantly lower incidence of second heart attacks. Their death rate was lower and fewer needed treatment to reopen

[10] For example, the Stem Cell Biology Laboratory at the Wolfson Centre for Age-Related Diseases of the King's College London, University of London, UK (Prof. Stephen Minger) or the Hadassah Embryonic Stem Cell Research Centre in Jerusalem (Dr Nissim Benvenisty)

blocked blood vessels. A smaller trial was carried out on 75 patients by German researchers where some received stem cells and others injections of a molecule that stimulates stem cell growth. The researchers reported that the treatment produced moderate but significant improvement in the injection fraction after three months.
In sharp contrast, the Norwegian study of 100 heart attack patients, half of whom received stem cells, showed no beneficial effect. There was no improvement in injection fraction, the amount of heart muscle damage, and the incidence of adverse effects was the same for patients who did or did not get stem cell therapy.

(U.S. Health and Human Service Department, 2006: www.healthfinder.gov)

Intersectorial small and medium companies (SMEs) are proliferating through joint ventures among clinicians, researchers and technology-based businesses, in different areas such as cord blood cell banking (Richard Branson, Virgin Cooperation, UK and recently in Monthey (VS), Switzerland), therapeutics for diabetes (Gameda, Ltd., Israel), therapeutics and cell expansion technology (Geron, USA). The UK and Israel are leaders in stem cell based therapies and are currently promoting clinical trials, especially in Israel where the religious concept of life does not restrict embryo stem cell research as much as in Christian countries. Slovenia is progressing steadily in the area of clinical use of mesenchymal stem cells (MSCs) in the area of cartilage and bone reconstruction with emphasis on exploitation. In Switzerland, Research Centres are developing rapidly in Universities and in private venture labs or start ups which increasingly engage in joint ventures to test stem cells in clinical trials. Countries who are not adapting their stem cell technology rapidly are quickly losing competence as this field is in full expansion. Good governance has to be an integrative part in embryonic stem cell (ESC) research and clinical application. Therefore, further research and development is important to keep pace with new findings and potential clinical applications. Often ethical debates have disproportionately hindered research designs to the point where cell clusters are more protected legally than newborn babies.

The European Commission (EC) has put a great deal of emphasis on stem cell research in its former programmes. Recently, on 29 March 2007, the EC has agreed to fund the creation of a *European registry for human embryonic stem cell lines*. This registry will provide comprehensive information on all human embryonic stem cell lines available in Europe (with details of source and

contacts) and will be publicly accessible through an internet site with high quality data and developments, such as clinical trials. The project has been accepted for 3 years with EU funding with one million Euros: "The EU is 100% committed to the highest possible standards of ethics in its research programme and this includes the use of human embryonic stem cells. We have a strict and transparent environment in place for their use in our programme", said European Science and Research Commissioner Janez Potočnik, "This registry plays an important part, making the most effective use of existing stem cell lines and avoiding the unnecessary creation of new ones. It will also be useful in the creation of common international standardisation for the characterisation of these stem cells, essential for progress towards new cures and therapies."[11] The U.S. government has also recently initiated a similar registry which is already functional on line.[12] Stem cell research is a very promising area for medicine to improve quality of life and healthy life expectancy. As Dr Nissim Benvenisty, head of the Department of Genetics at the Life Sciences Institute of the Hebrew University concluded as he briefed the Capitol Hill on stem cell in 2005: "We are in special days where we can do real pioneering research; we call it 'the cell that can do everything'. It can generate every cell in our body, while, at the same time, it is involved in so many aspects of human medicine. I am sure it will revolutionise the way we will do research and also transplantation medicine."[13]

Clinical translation of cell-based therapies is strongly emphasised by medical bodies at the EC; the involvement of small and medium enterprises will lead in the short terms to improvement of patients' quality of life. From that point of view cell-based therapies are offering serious solutions for the patient and society as a whole reducing side effects and health care costs, hence widely applicable to the low and medium-income countries. Therefore major patient organisation leaders, such as those chaired by the renown Mary Baker,[14] are promoting in agreement with the EC, patient initiatives due to stem cell

[11] For more information: http://www.ec.europa.eu/research/fp6/index_en.cfm?p=1_stem_projects

[12] http://stemcells.nih.gov/research/registry

[13] Israel: Stem-Cell Researchers in Israel Eye Debate in Washington, by Dina Kraft, United Jewish Communities News, 15 June 2007. (http://www.ujc.org)

[14] Mary G. Baker, MBE, is board member of the European Brain Council, President of the European Federation of Neurological Associations (EFNA), President of the European Parkinson's Disease Association and a consultant to the WHO and Chair of the WHO's Working Group on Parkinson's Disease. She is Director at Large for the World Stroke Association, Chair of the British Medical Journal (BMJ)'s Patient Advisory Group and a member of the management board of the European Agency for the Evaluation of Medicinal Products.

technology with the specific aim to foster dialogue with researchers, clinicians, the private sector and policy-makers for an objective evaluation of stem cell therapy following patient request.

In view of the promising therapeutic development, increasing collaboration and support has developed with patients who could benefit from stem cell therapy and tremendously improve their quality of life. This has triggered an enormous demand from patient organisations to work on further research and apply new findings. Society demands innovative and promising solutions with respect to quality of life and health cost reduction by avoiding the classical pharmacological interventions for chronic diseases with all the side effects for the patients. Mary Baker, President of the European Federation of Neurological Associations (EFNA),[15] at the first East England Stem Cell Network Symposium in 2006 confirmed that research is pursued in a wide variety of places but countries should give more support to such an important area, which she described as having a 'curiously uncertain future' as scientists and researchers, because of the controversial nature of the research, must always 'step back' to look at ethical issues. She underlines that "there is a need to improve the dialogue between scientists involved and patients. There should be no false claims and therefore no false hopes. There is also a need for a central database of what is going on and where it is taking place. Funds will need to be available for patients with rare disorders to go to countries where they can be treated. Patients need to be less competitive in terms of their desires for treatment for their particular condition."

The study of stem cells holds exciting promises, in particular for treating what is today incurable, e.g. traumatic injuries and degenerative diseases. It has led to inspiring discoveries for the future, which for now necessitate monitoring and caution as to the consequences on an ageing organism. The natural course of ageing, undeniably in association with cancer, is not lost in a stem cell despite its amazing ability to self-renew and restore some tissues in times of need (Bell and Zant, 2006). Even if the fact that research and funding for ESCs have been restricted in many countries, Switzerland holds a privileged regulation for research using ESCs under precise conditions. Researchers are currently working on methods to easily and reproducibly manipulate stem cells so that they possess the necessary characteristics for successful differentiation, transplantation, and engraftment. According to NIH, in order to bring successful

[15] http://www.efna.net

cell-based treatments to clinical practice stem cells must go through may steps and be reproducibly made to: proliferate extensively and generate sufficient quantities of tissue, differentiate into the desired cell type(s), survive in the recipient after transplant, integrate into the surrounding tissue after transplant, function appropriately for the duration of the recipient's life, and avoid harming the recipient in any way. To avoid the problem of immune rejection, scientists are also experimenting with different research strategies to generate tissues that will not be rejected.

In 2006, 60 researchers, ethicists, scientific journal editors, and lawyers from 14 countries met in Hinxton (UK) to produce a set of global guidelines for stem cell research, which they hope will aid collaboration and progress in the field, but also set international standards that will soften restrictive government regulations so international collaboration and publications can take place.[16]

Functional intelligent biomaterials: Future stem cell therapy developments will also involve the use of 'intelligent biomaterials' and new forms of 'biosurgery'. Functional development such as hydrogels (e.g. three-dimensional polymer networks forming porous matrices) has significant clinical potential: it addresses critical issues in cell-based therapy in regenerative medicine for tissue regeneration and organ repair. Such biomaterials are designed to support the development of stem cells, and by providing a 3D scaffold to allow formation of tissue architecture. Basic requirement of such biomaterials include safety and efficacy with tissue-building properties for cell recruitment and organisation, and the introduction of biologically active agents to enable control over proliferation and differentiation of stem cells. Functional polymeric biomaterials are therefore useful when combined with stem cell (i) in vitro, for the production of tissue-engineering scaffolds, and (ii) in vivo, as an artificial niche for the recruitment and differentiation of endogenous stem cells and progenitors to stimulate organ self-repair. The use of functional and active biomaterials for therapeutic applications, in combination with stem cells, opens a new area in reconstructive surgery and should be encouraged in parallel to stem cell therapy clinical trials (Woerly, 2000, 2007).

[16] Cf Digital Journal, 3 March 2006, Global Stem Cell Research Guidelines created by expert panel (the Hinxton group): http://www.digitaljournal.com/news/?articleID=4469

Conclusion: Consistent evidence exists in animal models that stem cells targeted to specific cell types generate new cells and tissues. This gives a wide range of possibilities for treatment of degenerative or other age-related diseases such as Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, rheumatoid arthritis and chronic heart disease. It also holds promises in tissue engineering due to growing new organs for transplantation and solves the issue of organ supplies from donors.

Stem cells are being used in many areas of anti-ageing research and development for direct application in the case of different age-related ailments, and small number trials have shown positive findings.

Risks: Remains to be consistently reproduced in humans before safe clinical application. For the moment, besides ASC therapy for artificial retinal, heart tissues or cartilage, stem cell therapy remains at high risk of uncontrollable proliferation of cancer cells.

Recommendations: The promise of stem cell therapies is an exciting one, but significant technical hurdles remain that will only be overcome through intensive research and international collaboration.

Clinics that have offered cell-therapies for many years ought to report regularly their findings to the scientific community in order to share their knowledge on what works and what does not.

However, for the time being there is no recommendation for routine use in clinical practice. While clinical cases have shown improvement, larger trials are needed to show the impact on the quality of life and the reduced endpoints such as second heart attacks, deaths, and renewed hospitalisations.

Patient's perspective: There is a need for a stronger voice and for more transparency between scientists and patients as to results and applications. The right to health and access to stem cells will eventually become a key issue for ensuring treatment of the most in need and vulnerable of society. In this perspective, while respecting culture and religious beliefs for ESC, everyone should be able to access future adult or cord blood based stem cell therapy.

Ethical issues: Adults stem cell research and therapy does not pause a critical ethical question. In contrast, the use and abuse of embryonic stem cells is a concern, which has led many governments to restrict stem cell

research because of the 'Right to Life' issue. The protection or scientific use of cell clusters beyond newborns is subject to fundamental ethical debate and is often dependant on religion. Beside the importance of the intention leading to stem cell use, the concept of when starts ad when ends Human Life varies from one religion to the other: while some religions are in favour, others reject embryo stem cell research and therapy.[17] The ethical debate should also focus on accessibility and affordability of regenerative medicine for all people to avoid the development of therapies for the privileged only.

Other cell therapies have been used for several decades to the satisfaction of clients like at the world renowned Clinique La Prairie in Montreux (Switzerland). Other clinics, such as the Mita Clinic in Tokyo (Japan), have been developing a private practice offering exclusive cell therapy based on the retrieval of skin cells (behind the ear) which are deposited in a 'Cell Bank' with personal attribution. Those cells can then be 'cultivated' in vitro and re-injected into different locations of the skin for rejuvenation of the person at any age. The efficacy is measured through visual and subjective measurements in terms of pre- and post-images of the skin, as well as the client satisfaction. According to Mita Clinic doctors, treating young patients with his cells or an older patient with his 'young cells' kept in the cell bank holds more guarantee that the treatment will show results: the younger the patient's cell, the more efficient will the cell-based treatment be, therefore it is strongly encouraged to bring one's cells to the bank at younger ages.

[17] For the Catholics, the principle of Life is that the human soul is created by God at the moment of conception, therefore there is strong opposition to embryonic stem cell research; for most Muslim traditions, a gradual development of personhood leads to 'ensoulment' after 40 days of conception; Judaism teaches the basic premise that moral status is acquired, it is not there from the beginning: "40 days marks a morally significant point … [thereafter, the embryo] becomes something more significant", which is reflected by the widespread Jewish support for stem cell research further supported by the high regard placed on healing and on the good of medicine. The Moral Status of the Embryo, Harvard Magazine (September-October 2007): http://www.harvardmagazine.com/2007/05/the-moral-status-of-the.html

5.4. Gene Therapy, Genomics, Proteomics and Predictive Medicine

Background: Although gene therapy research started clinical trials in the 1990s already, it is still at an experimental stage; only recently have some successful cases been described, but it remains a highly polemic area of intervention for the human species. The objective of gene therapy is to treat, cure or ultimately prevent disease by changing the expression of a person's genes. Gene therapy can be targeted to somatic (body) or germ (egg and sperm) cells. In somatic gene therapy the recipient's genome is changed, but the change is not passed along to the next generation. In germline gene therapy, the parent's egg or sperm cells are changed with the goal of passing on the changes to their offspring. Germline gene therapy is not being actively investigated, at least in larger animals and humans, although discussion is intense over its value and desirability.

(The Human Genome Project – RIKEN Genomic Sciences Centre, Japan)

5.4.1. Gene Therapy and Longevity

Gene therapy relies on similar principles as traditional pharmacological therapy; regional specificity for the targeted tissue, specificity of the introduced gene functions in relation to disease, and stability and controllability of expression of the introduced gene. Gene therapy can be performed either by direct transfer of genes into the patient or by using 'vectors', in most cases viruses, as vehicles to transport the genes of interest. Both modes have certain advantages and disadvantages. Direct gene transfer is particularly attractive because of its relative simplicity. Because of bio-safety concerns, the viruses are typically altered so that they are not toxic or infectious (that is, they are replication-incompetent). These basic tools of gene therapists have been extensively optimised over the past 10 years.

Scientific evidence of the genetic manipulation to extend life: In their review article on 'Genes That Prolong Life and the Relationships of Growth Hormone and Growth to Ageing and Life Span' Andrzej Bartke and his colleagues (2001) state that studies in yeast, worms, and flies have provided considerable evidence for the existence of genes that control ageing and life span. At least 15 different genetic manipulations induce life extension in organisms such as fruit flies, nematodes, and mice meaning that increases in life expectancy in animal models can be accomplished genetically (table 6; Miller, 1999; Guarente and Kenyon, 2000).

Although such genes have been identified, it is not always obvious how the proteins coded by these genes are involved in the determination of longevity. These exciting developments raise obvious questions as to the extent the findings obtained in these organisms may be relevant to vertebrates and especially to mammals and to humans.

Scientific evidence: Gene therapy is still in its infancy as most human clinical trials are still at the experimental stage. It has the potential to become an important treatment regimen by countering genetic diseases with short life expectancy such as cystic fibrosis. In principle it allows the transfer of new genetic information into patient tissues and organs. Consequently, diseased genes can be eliminated or their normal functions rescued. Furthermore, the transfer procedure of genetic materials allows the addition of new functions to cells such as the production of immune system mediator proteins. Today, new hopes for controlled and specific genetic manipulation have arisen with the potential use of human embryonic stem cells. The human embryonic stem cells could be genetically manipulated to introduce the therapeutic gene. This gene may either be active or awaiting later activation once the modified embryonic stem cell has differentiated into the desired cell type. Despite these hopes, some warning cases involving gene therapy show a high risk of genetic manipulation or epigenetic consequences (see box below).

Three warning cases about gene therapy

1) *Jesse Gelsinger case, first gene therapy victim (1999):* Jesse was 18 years old and had a rare genetic disease, known as ornithine transcarbamylase (OTC) deficiency. It affects his ability to rid his body of ammonia, a usual, but toxic breakdown product of protein. Half of the children with OTC die in their first month of life, and half die before their 5th birthday. Jesse had a mild form of the disease because some of his enzymes were functioning normally. He was able to control the disease with diet and drugs, though he needed to take 32 pills a day. On 13 September 1999 Jesse received an injection of 30 milliliters of the adenovirus with the corrective OTC gene which provoked a immune system reaction leading to multiple-organ-system failure. Jesse died 4 days after the gene-therapy injection, as a result of his voluntary participation in a gene-therapy experiment, becoming the first known human victim of this technology. Jesse's experience illuminates important elements that should make government agencies, scientists, and the public regulate and oversee this technology very seriously (Kolehmainen, 2000).[18]

[18] For further details, see http://www.actionbioscience.org/biotech/kolehmainen.html

2) *The first successful clinical trials using gene therapy* to treat a monogenic disorder involved a different type of SCID (severe combined immunodeficiency) caused by mutation of an X chromosome-linked lymphocyte growth factor receptor (Hacein-Bey-Abina et al., 2002, 2003). While the positive therapeutic outcome was celebrated as a breakthrough for gene therapy, a serious consequence set all aback: by February 2005, three children out of seventeen who had been successfully treated developed leukaemia because the vector inserted near an oncogene (a cancer-causing gene), inadvertently causing it to be inappropriately was expressed in the genetically-engineered lymphocyte target cell.

3) *'Inadvertent' germline gene transfer:* In 2001, scientists confirmed the birth of some 30 genetically altered babies whose mothers had undergone a procedure called ooplasmic transfer.[19] In this process, doctors injected some of the contents of a healthy donor egg into an egg from a woman with infertility problems. The result is an egg with two types of mitochondria, which are cellular structures containing a tiny amount of DNA and which provide the energy for the cell. The babies born following this procedure thus have three genetic parents, since they carry DNA from the donor (a tiny amount due to mitochondrial DNA) as well as the mother and father. Although the researchers announced this as the "first case of human germline genetic modification", the gene transfer was an inadvertent side effect of the infertility procedure. However, the mixed mitochondrial DNA will be passed on to all future generations descending from these individuals.[20]

Genomics research is arousing the hope that interventions will be adaptable to an individuals' genetic profile. Genetic susceptibility to disease ranging from intestinal cancer to immune-system condition will be mapped and could facilitate individually-tailored interventions according to the personal genetic constitution. In the near future, consumers will be choosing their treatment and dietary supplement on the basis of their own genetic constitution. The genetic profiling studies a number of genes and specifically examines variations called polymorphisms (determining an individuals' unique features as well as the internal body functions). A gene profile can predict predisposition to many health/disease conditions.

[19] *Ooplasmic transfer:* experimental fertility technique that involves injecting a small amount of ooplasm from eggs of fertile women into eggs of women whose fertility is compromised. The modified egg is then fertilised with sperm and implanted in the uterus of the woman attempting to achieve pregnancy. See http://www.geneticsandsociety.org/article.php?id=381

[20] Source: The Human Genome Project, RIKEN Genomic Sciences Centre, Japan

Table 6: Genes Influencing Life Expectancy in Animals

GENE	ORGANISM	BIOCHEMICAL FUNCTION	COMMENTS
v-Ha-RAS	Yeast	Oncogene	Life expectancy varies with level of expression
lag1	Yeast	Ceramide signaling pathway	Mutations increase life expectancy
sir2	Yeast	NAD-dependent histone deacetylase	Activity required for normal life expectancy; over-expression increases life expectancy
daf2	Nematode	Insulin/IGF-I like receptor	First step in insulin-like signaling pathway; mutations increase life expectancy
age1/ daf23	Nematode	PI-3-kinase	Operates in insulin-like signaling pathway: mutations increase life expectancy
daf16	Nematode	Transcription factor	Expression required for life expectancy extension by daf2 or daf23 mutations
tkr1	Nematode	Tyrosine kinase	Over-expression increases life expectancy and resistance to stress
InR	Fruit fly	Insulin/IGF-I like receptor	First step in insulin-like signaling pathway; mutations increase life expectancy
chico	Fruit fly	Insulin receptor substrate	Second step in insulin-like signaling pathway; mutations increase life expectancy
mth	Fruit fly	Transmembrane protein	Partial loss of function increases life expectancy and resistance to stress
indy	Fruit fly	Dicarboxylic acid transport protein	Partial loss of function increases life expectancy
SOD-1	Fruit fly	Cu/Zn-superoxide dismutase	Over-expression increases life expectancy
p66shc	Mouse	Not known	Mutations enhance resistance to apoptosis and increase life expectancy
pit1/ prop1	Mouse	Required for pituitary development	Mice are deficient in GH, prolactin and TSH, and grow slowly; mutations increase life expectancy; delayed immune and collagen aging
ghr/bp	Mouse	Growth hormone receptor	Loss of function increases life expectancy

Source: International Longevity Centre New York, 2001

5.4.2. Genomics, Polymorphism and Genetic Passport

> *Genomics* is the characterisation and sequencing of an organism's genome and the analysis of the relationship between gene activity and cell function. The goal of genomics is to determine the complete DNA sequence for all the genetic material contained in an organism's complete genome. *Functional genomics* (sometimes referred to as functional proteomics) aims at determining the function of the proteome (the protein complement encoded by an organism's entire genome). It expands the scope of biological investigation from studying single genes or proteins to studying all genes or proteins at once in a systematic fashion, using large-scale experimental methodologies combined with statistical analysis of the results. *Structural genomics* is the systematic effort to gain a complete structural description of a defined set of molecules, ultimately for an organism's entire proteome. Structural genomics projects apply X-ray crystallography and nuclear magnetic resonance spectroscopy (NMR) in a high-through put manner.
>
> (Definition from Institute Pasteur, Paris[21])

Some anti-ageing clinics are already offering a genetic passport for their patients to maximise therapeutic success of interventions through what they call the 'Gene Predict Clinic': "We invite you to obtain your genetic passport—a profile—that will lead to tailor-made treatments, effective medications (without side-effects) and slowed ageing process in one of the safest and discrete countries in the world, Switzerland." This service is outsourced to Gene Switzerland which affirms readily that it can "predict how you are likely to respond to environment, food, stress, pregnancy, menopause/andropause, medications and much more."[22] Other such services are blossoming around the world claiming scientific back-up and pools of highly elaborated technologies (e.g. www.genialgenetics.com).

[21] http://www.pasteur.fr/recherche/unites/Binfs/definition/bioinformatics_definition.html
[22] http://www.switzerlandclinics.com/swiss-clinics/Gene-clinic

Polymorphism and Preventive Medicine

"Individualised medicine has become a catchword in the medical environment. Is it possible to use the diagnosis of genetic polymorphisms to assist and help individualised Hormone Replacement Therapy (HRT)? Functional genetic polymorphisms are important in our effort to individualise hormone replacement therapies. The problems of the never-ending story are not the hormones—the products from Mother Nature—, the main problem is the unprofessional and un-individualised prescribing of hormones. It is morally and intellectually unacceptable to prescribe the same oestrogen dosage to hundreds and thousands of female patients. This is not the case in the replacement of other hormones such as thyroid hormones or insulin and must be respected also in the replacement of sexual steroids. Functional genetic polymorphisms in hormone metabolising and synthesising enzymes are a wonderful tool for the individualised hormone replacement therapy.

Can the knowledge of genetic polymorphism help to create clarity? Yes, it can. Polymorphisms in the Androgen Receptor gene, the Vitamin D Receptor gene, the Progesterone Receptor gene or the TGFBR1 gene for example become more and more important for advising female patients. Knowledge of this polymorphism helps physicians in evaluating individual risks of breast cancer. Finally, what about the future: What significance will the diagnosis of genetic polymorphisms have in the near or distant future?"

(Prof. Johannes Huber, Founder of the European AAM Association)

The development of predictive medicine and new predictors of disease are based on tests that detect that 'something is wrong' or 'could go wrong' like in mapping genes. As technology is evolving so are promises in predicting risk for specific conditions, which is the case for example, of proteomics for the risk of cancer and other ailments (Powell, 2003).

The Proteome is the protein complement expressed by a genome. While the genome is static, the proteome continually changes in response to external and internal events. Proteomics aims at quantifying the expression levels of the complete protein complement (the proteome) in a cell at any given time. While proteomics research was initially focused on two-dimensional gel electrophoresis for protein separation and identification, proteomics now refers to any procedure that characterises the function of large sets of proteins. It is thus often used as a synonym for functional genomics.

(Definition from Institute Pasteur, Paris)

Proteomics has attracted scientists for its role in understanding an organism more than genomics. Since proteins play a central role in the life of an organism, proteomics is instrumental in the discovery of biomarkers, such as markers that indicate a particular disease. This interest is supported by recent funding and the creation of new academic centres such as the Harvard Institute of Proteomics (HIP) in fall 2006, which includes the site of the Protein Structure Initiative Materials Repository (PSI-MR), funded by NIH and the National Institute of General Medical Sciences. The Human Genome Project completed the human genome sequence in 2003 (Collins et al., 2003) and established about 20,000 to 25,000 genes vs. about 1,000,000 proteins. The count of genes and proteins is still evolving and recently in May 2007 at the Biology of Genomes meeting in New York it was reported that humans may have only 20,488 genes, with perhaps 100 more yet to be discovered (Pennisi, 2007). Thus, establishing an 'Atlas' or 'Catalogue' of all human genes and proteins, their functions and interactions is a great challenge for scientists. An international collaboration with these goals is co-ordinated by the Human Proteome Organisation (HUPO – www.hupo.org).

5.4.3. From Genomics to Proteomics: Tools for Predictive Medicine

Today new predictors of diseases are being discussed at the biomolecular level; for example, molecules called 'predictive autoantibodies' in the blood, if detected, could warn the doctors that a patient is 'brewing' certain diseases and may even indicate roughly how soon the individual will begin to feel symptoms, which will allow them to take preventive action (Scientific American, Notkins, March 2007).

The debate on predictive medicine is also quite 'hot' in the area of genetics where predictions on the number of genes yet to be found is in constant evolution; the researchers in this field put great hope in opening the door to early detection of potential system failure in the near future. For example, the U.S. National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH), announced in August 2007 grants expected to total approximately $30 million to establish one new Centre of Excellence in Genomic Science at the Dana-Farber Cancer Institute (DFCI). The centre's ultimate goal is "to develop general principles for data integration and network prediction. The knowledge gained will be used to develop better models to interpret genome-wide genetic variations in the context of human disease".[23]

[23] For further details, see http://www.genome.gov

The portrayers of predictive antibodies underline that chronic diseases arise form a complex interplay between environmental influences and multiple genes (each of which makes a small contribution to a disease). So detection of susceptibility genes would not necessarily reveal with any certainty whether or when an individual will come down with a particular autoimmune condition. In contrast, detection of specific autoantibodies would signal that a disease-causing process was already underway. Ten or 20 years from now, autoantibody screening for at least some disease will almost certainly become a familiar part of the standard medical examination, bringing an interesting biomarker for disease (Notkins, 2007).

List of Ethical Problems to Consider when Predicting a Future Risk to Patients

Before developing predictors of diseases and foretelling a patient's risk of future disease, Notkins (2007) underlines ethical and practical issues to consider:

- Should doctors test for diseases that have no preventive treatment or cure?
- What is the best way to make sure patients understand that a positive test does not mean 'disease will definitely develop' but rather, indicates a 'given probability of risk'?
- How can the risks of false positive or negative tests be minimised so that few patients are unnecessarily alarmed or mistakenly reassured?
- Is the cost of routine screening justified by the number of patients who would be found to be at risk and able to benefit from early treatment?
- For autoimmune diseases that run in families, should family members of afflicted individuals be tested and will the worry over a result indicating a high risk of developing the disease be easier to live with than the anxiety of not knowing?
- Will a positive test lead to discrimination from employers, health insurers, or society in general?

Predictive medicine has a bright future ahead not only for professionals but for patients and consumers themselves. Often mentioned as 'personal predictive medicine', the anti-ageing medicine movement is harnessing many of the newest health technology tools to identify at the 'earliest stage' any imbalance or disease in order to intervene. The melted pot of anti-ageing followers is bringing together persons from all fields, including patients and consumers who

wish to know more. Therefore new terms are flourishing in this area such as 'bio-scaler technology', 'bio-focus for cancer detection' or 'integrative addictionology'.

Conclusion:

a) *Genetic manipulation, genetic therapy:* Convincing evidence in animal models suggest that genetic manipulation extends the life span. The promise of the technology is great and the reality of it is very dangerous. Successful clinical cases were short lived with high rates of subsequent mortality. At this stage of scientific progress and experimentation, no data can favour application to human subjects, and even more so to healthy persons for the sole purpose of life extension or AAM.

b) *Genetic diagnostics, predictive medicine:* The development of predictive medicine is an exploration into knowing better the human species. The completion of the Human Genome sequencing in 2003, a high-quality comprehensive sequence of the human genome has made genomics a reality.

Risks: There is evidence in humans that genetic manipulation and gene therapy can be lethal. With the present state of scientific knowledge, gene therapy is still a risk and holds serious safety issues for life, health and emergence of unknown outcome. Furthermore, many areas remain unknown: for example, would the genes related to ageing in flies or mice be similar suitable targets for experimental manipulation in the 'human versions'? What are the consequences of gene interactions linked to the unpredictable developments subsequent to genetic manipulation? Despite the great promises of gene therapy and manipulation, many unsolved issues such as safety, deleterious consequences and ethical problems still exist. Strong surveillance and ethical guidelines are needed.

As for predictive medicine through genetic diagnostics, the ambition of the Human Genome Project to map all human genes lies above all in the management of the information provided. For example, genetic passports need to find a standard set of diagnosis criteria—clinics and practices need to be regulated. False promises to consumers must be avoided to anticipate future consequences of abuse and deviant diagnosis.

Ethical Issues:

a) *Human gene therapy experimentation* raises many ethical issues about changing life's mechanisms and engineering the DNA system carrying lineage and individual genetic information. There are important potential consequences in genetic manipulation, especially if those are irreversible for the future generations and the lineage, for descendants who had no right to decide upon this change. In contrast, some experts hold the view that genetic engineering will one day be of benefit for incurable diseases such as Alzheimer's disease or the Down Syndrome. As long as safety and lack of evidence remains, this latter ethical position will remain irrelevant.

b) *Predictive medicine* holds different ethical questions: how and for what purpose will the information on genetic mapping of individuals be used? Will it be beneficial or detrimental to the patient's protection and rights? Many issues remain without answers and need to be addressed by a multidisciplinary group of experts.

5.5. Pharmacological Interventions

Pharmacological interventions represent one of the most important segments of AAM and of the anti-ageing market, together with dermatological products. Therefore the presentation will be limited to the main products on the international market.

5.5.1. The Human Growth Hormone Paradox

Background: Growth Hormone (GH) or Somatotropin (STH) is a protein hormone which stimulates growth and cell reproduction in humans and other animals. The human body naturally produces growth hormones. Beginning in our 40s, the pituitary gland—the pea-sized structure at the base of the brain where growth hormones are made—gradually reduces the amount of hormones it produces. With age the reduced levels of GH have been assumed to be responsible for the frailty that typically comes with getting older. This leads more and more AAM protagonists and consumers growing old and feeling weak turn to injections of synthetic human growth hormone (HGH) to counter the realities of old age, despite the lack of consistent evidence.

GH is released from the anterior pituitary gland. Pituitary adenomas can produce excess GH. This can cause abnormal growth patterns called acromegaly in adults and gigantism in children. Excess GH can increase blood pressure, blood glucose and can be fatal. A GH test measures the amount of GH in the blood.
Synthetic HGH is available only on prescription and is administered through subcutaneous injections. It is currently possible and efficient to treat adults with true GH deficiency (caused by pituitary tumours among other causes) but not primarily prescribed to counter the signs of age-related decline. Synthetic HGH is also approved for children with short stature or with kidney failure, and for adults with muscle wasting associated with AIDS and HIV.

(The U.S. National Institute of Health and Mayo Clinic[24])

A serious concern in the search for combating age-related decline and degeneration is

(i) that while some interventions could have short-term benefits, they could also have long-term adverse effects;
(ii) that while some treatments are efficient in some patients, the same treatments can have no effects or adverse effects in others depending on different factors such as biological age, genetic predisposition, gender, health status or frailty;
(iii) that too strong or repetitive dosage may lead to serious irreversible consequences (e.g. abnormal growth of limbs, cancer cell proliferation).

The use of GH as an anti-ageing therapy has been reported as the most popular health-related internet search (Tsouvalas, 2006). Although the exact number of people who use GH as an anti-ageing therapy is unknown, Perls and his colleagues (2005) reported that 20,000 to 30,000 people used GH in the United States as an anti-ageing therapy in 2004 (Kaufman, 2002), a more than 10-fold increase since the mid-1990s (Perls and Olshansky, 2006).

In a thorough scientific review, Van der Lely (2004) demonstrates the difference between justified and unjustified use of GH. GH has become an accepted therapy for children and adults with GH deficiency due to a pituitary disorder.

[24] See http://www.nlm.nih.gov/medlineplus/ency/article/003706.htm and www.mayoclinic.com

According to the author, “GH is increasingly suggested, however, as a potential treatment for frailty, osteoporosis, morbid obesity, cardiac failure, and various catabolic conditions. […] However, it might even be dangerous to use excessive GH dosages in conditions in which the body has just decided to decrease GH actions. In contrast to GH replacement therapy in GH-deficient subjects, excessive GH action due to GH misuse seems to be ineffective and even dangerous. Moreover, there are no available study data to indicate that the use of GH for non-GH-deficient subjects should be advocated.”

The systematic review recently conducted by Liu et al. (2007) shows two different pictures of elderly people taking GH. Liu concludes that on one hand GH therapy has been shown to improve clinical outcomes and possibly decrease death in longitudinal studies of adults who are GH-deficient, on the other hand, little evidence of clinical benefits of GH therapy are found in the healthy elderly but rather high rates of adverse events. In GH-deficient populations, some adverse effects of this intervention were consistently identified in the review: higher proportions of soft tissue oedema and joint pain (not associated to dosage or age) and consequences related to fluid retention due to the effect of GH on fluid homeostasis. An interesting finding, which is confirmed for other hormonal interventions, is that women respond to GH therapy differently from men. Even with higher doses of GH per kilogram of body weight, women treated with GH do not increase lean body mass and achieve only significant borderline decreases in fat mass, whereas men treated with GH have significant improvements in both of these outcomes. Other differences have been found (e.g. differential decrease in lean body mass or fat mass, in soft tissue oedema), for a review, see for example: Liu et al., 2007. According to our survey, GH is administered successfully to patients in some clinical settings, in particular for older people in the post-surgery phase to avoid the significant muscle decrease due to the bed-ridden immobility.

Women may require higher doses of GH for longer periods than men to achieve physiologic replacement levels, which could underline a similar trend for other AAM interventions. These findings suggest that men and women respond differently to GH in terms of body composition and adverse events so that further research is needed to fully explore the risks and benefits of GH therapy based on sex; this applies equally to research on animals and on humans. Due to methodological problems and variable quality of cumulative literature published on randomised controlled trials evaluating GH in the healthy elderly, results of research cannot be generalised to the population or to sub-groups by

age, sex, health status, etc. (e.g. missing data on functional performance, psychosocial or subjective measures, too few participants with heterogeneous profiles or risk of non-measured correlated factors). Further well-designed research is needed before GH supplementation in humans can be considered as either safe or useful for long-term intervention.

As anti-ageing medicine promotes it, GH is a powerful anabolic hormone that affects all body systems. Despite its side effects and lack of precise evidence for its efficacy, the use of GH for performance enhancement purposes has increased in amateur and professional sportsmen and sportswomen, in particular, to improve athletic performance or to enhance appearance (Hulten et al. 2001). The lack of official systematic testing for GH doping (discussion is currently going on to implement such a test) together with the widespread rumours of its tremendous beneficial effects, seem to make this compound attractive for athletes, especially runners and professional cyclists. However, the International Longevity Centre (2001) also recommends and encourages the use of GH as an anti-ageing intervention without any details as for which conditions and for which patients.

According to the Mayo Clinic,[25] "some websites claim to sell a pill form of human growth hormone that produces results similar to its injected form. Sometimes these are called human growth hormone releasers. There's no proof that these claims are true. In fact, if you were to swallow human growth hormone it would probably be digested by your stomach acids and not absorbed into your body. Websites also sell homeopathic remedies claiming to contain human growth hormone. There is no proof of their effectiveness either."

A4M message on Human Growth Hormones (HGH)

"Most people think of HGH as the miraculous treatment for children doomed to dwarfism, which over the past thirty years has saved tens of thousands from this fate. The next great benefit of HGH therapy appears to be in the ageing population. People with age-related deficiency of HGH become overweight, flabby, frail, and lethargic; lose interest in sex; have trouble sleeping, concentrating, and remembering things; tire easily; and

[25] Mayo Clinic is a not-for-profit medical practice dedicated to the diagnosis and treatment of virtually every type of complex illness in three locations in the USA (Arizona, Minnesota, Florida). It includes the expertise of 2,500 physicians and scientists providing not only clinical treatment, but also medical research and education. See http://www.mayoclinic.com

> in general, lose their zest for life. With HGH, all these so-called signs of ageing can be reversed. Indeed, nearly 20,000 clinical studies conducted around the world document the broad benefits of pharmacological HGH therapy. These studies suggest a wide range of effects when HGH is replaced: reduced body fat, increased muscle mass, higher energy levels, enhanced sexual performance, regrowth of vital organs, restoration of youthful immune function, stronger bones, lower cholesterol and blood pressure, faster wound healing, smoother and firmer skin, regrowth of hair, sharper vision, elevated mood, improved cognition."
>
> (By the AAM founders Klatz and Goldman, 2003:61–62)

Synthetic Production of HGH

The Federal Drug Administration (FDA) approved HGH for use in adult patients only in 1996.[26] Before that date HGH was authorised only for HGH-deficient children.[27] In effect, the FDA approval covers the use of HGH for anti-ageing purposes since low levels of HGH or IGF-1 indicate a failure of the pituitary. This approval means that any physician may now prescribe HGH for adults without fear of practicing outside of conventional orthodox mainstream medicine. Today, HGH is administered by injection (under the skin) which is considered by patients as easy to do. In June 2000, *Genetech, Inc.* and *Alkermes, Inc.* announced availability of the first long-acting dosage form of recombinant HGH.

[26] On 23 October 1996, Somatropin, a type of synthetic human growth hormone also known as Genotropin or Serostim, was approved by the FDA for HIV/AIDS treatment. Somatropin stimulates growth of the long bones in the arms and legs by affecting growth of cartilage, bone, and muscle cells, but also increases the size of body organs and increases the number of red blood cells. It is used to maintain lean body mass of patients in the hopes of improving overall health. GH can only be legally prescribed for the aforementioned purposes approved by the FDA; however, many off-label uses for the hormone exist, such as athletic performance enhancement and anti-ageing treatment.
http://aidsinfo.nih.gov/DrugsNew/DrugDetailNT.aspx?int_id=0327

[27] On 8 March 2007, FDA approved human growth hormone (trade name Humatrope) manufactured by Eli Lilly Co. of Indianapolis. Its approved indications are only for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.
http://www.fda.gov/bbs/topics/ANSWERS/ANS00319.html

Conclusion: The use of GH in non-GH-deficient subjects is not recommended. Taking HGH can cause a number of side effects. However, it is widely taken by adults, either for anti-ageing or by athletes to improve their performance artificially.

Despite successful clinical cases, GH-deficiency in older persons is a source of concern: clinical studies and research is required to determine the conditions to which it applies and the appropriate dosage according to age, gender and health status.

In healthy ageing subjects, treatment to improve muscle mass and/or strength through the use of GH should be conducted under medical supervision to avoid misuse and side effects of GH.

Medical professionals should be better informed and in contact with endocrinologists and sports doctors to improve knowledge and gather experience in this field. The differential effect men-women should also be taken into consideration in research and medical practice.

The use of GH in patients with severe diseases in intensive care setting has been shown to be dangerous and should definitely be carried out only under strict medical supervision.

5.5.2. Hormones: Dehydroepiandrosterone (DHEA)

Background: DHEA (adrenal hormone dehydroepiandrosterone) and DHEAS (its sulphated ester) are steroid hormones present in both male and female. As for other hormones, blood levels are high in young adults and decrease with advancing age. There is some epidemiological evidence that relatively high serum DHEAS levels in males may protect against heart disease. In the USA, DHEA is sold freely over the counter and on internet. Sales have increased since the 1990s and there is still growing public enthusiasm for DHEA supplementation to slow down the ageing process as well as age-associated cognitive impairment. However, there is very little evidence from controlled trials.

(Cochrane systematic review by Grimley Evans et al., 2006)

The principle of anti-ageing medicine is based on the observation of decreased levels of metabolic compounds with age taking ‘youth level’ as the ‘Golden standard’ of an optimal body composition which allows peak performance, bodily activation and functionality. It is therefore tempting to believe that

restoration of hormone levels to those that exist in young persons would bring benefits to one's health, vigour, and vitality. This approach is adopted by many adepts with regards to DHEA. However, hormone replacement therapy is a long-term intervention, possibly continuing for the rest of a patient's life, and is impossible today to exclude some unexpected and unknown undesirable effects.

Supplementation with melatonin or DHEA, or with injection of GH, has been promoted by different authors (Regelson and Colman, 1996). The question is, however still contradictory and controversial. A Cochrane systematic review conducted on the effect of DHEA on cognitive function in healthy elderly people (Grimley Evans et al., 2006) concluded that there was little evidence of beneficial effects of DHEA supplementation, but also little evidence from the randomised controlled trials that DHEA produces any adverse effects. Adverse effects seem more linked to the market safety than to the substance *per se,* to the free distribution of DHEA. In most countries like the USA, DHEA is considered as dietary supplement and not as pharmacological substance, hence controls are not as strict. For example, the validity of the amount and quality of DHEA mentioned in the product can be questionable. Thus, as Meier points out (2002), the danger lies in the many unknown dangerous compounds and uncontrolled substances manufactured under the label of DHEA, which can easily be acquired by Swiss citizens through tourism or internet shopping.

Prof. Etienne-Emile Baulieu, known for inventing the RU486 abortion pill in the 1980s as well as his clear position on DHEA efficiency, conducted conclusive researches on the benefits of DHEA (e.g. Baulieu, 1996; Baulieu et al., 2000), was interviewed for this report and underlined the systematic positive results of his experimental and clinical studies on the effects of DHEA, especially in men (findings: positive effects of 50mg of DHEA on 280 participants during a year on bone mass, skin thickness and pigmentation, and libido). He also warned on the falsification of DHEA products which he observed in another study conducted on a dozen of DHEA products where he found very few that actually really contained DHEA. Thus, researches conducted with AAM products must first and before all control the content validity of the product tested. While research on anti-ageing is not an ethical issue in his view, yet an key issue arises more from manufacturing DHEA products with misleading labels, e.g. with no or little DHEA substance while advertising promises a given amount and subsequent benefits with warning for specific groups. Monitoring manufactured AAM products and their claims is therefore an important safety issue.

Conclusion: There is no consistent evidence of benefits or adverse effects. Further research is needed, but more specifically thorough methodological design which avoids heterogeneous samples, short-term follow-up and confounding or absent factors from the studies. More representative samples of men/women and control on the different dosages are needed. The reviewers recommend, in the light of growing public enthusiasm for DHEA supplementation, to further clinical trials in which the DHEA treatment lasts for over one year and the number of participants is large enough to allow relevant statistical analysis.

5.5.3. Female Hormones: Hormone Replacement Therapy

Background: Hormone therapy for menopause has also been called hormone replacement therapy (HRT). Lower hormone levels in menopause may lead to hot flashes, vaginal dryness and thinning of the bones. To remedy these problems, women are often given oestrogen or oestrogen with progestin, another hormone.
The development of HRT for women illustrates well the difficulty of building evidence for large-scale population interventions. As what AAM claims for other less known hormones, HRT is the typical place of supplementing for a hormonal deficiency known in women through menopause and can make the case for the complexity of scientific findings in clinical or routine interventions for age-related conditions.

Sex steroid hormones are believed to provide women with protection against diseases such as cerebrovascular events. This idea is corroborated by the facts that i) premenopausal women have a lower risk of stroke than men of the same age (Barrett-Connor and Bush, 1991) and ii) the incidence of stroke in women increases rapidly after menopause (Wenger et al., 1993), together with diminished circulating levels of oestrogen and progesterone. As a result, HRT has been used widely not only for vascular prophylaxis, but also because it reduces menopausal symptoms. However meta-analyses of observational studies have suggested that HRT may increase the risk of stroke, especially ischaemic stroke (e.g. Bath and Gray, 2005). Furthermore, the results of randomised controlled trials have given conflicting results either finding no benefit or some apparent hazard.

These observations add to a rapidly expanding literature on the potential hazards and benefits of the therapy (Grady, 2003). In the USA, the Women's Health Initiative (WHI) trial, a large scale study with 27,000 women (see box below), indicated an increased risk of ischemic strokes in women in all risk categories and not just those judged to be at high risk; "the monotherapy arm (oestrogen alone, for women without an uterus) of the trial was also ended early because of an increase in non-fatal strokes. Full details from the sub-group analysis of this second arm are not yet available, and the evaluations of the low fat diet and calcium supplements are continuing" (Crawford and Langhorn, 2005). The WHI results had an immediate impact on the market: when the conclusions of the study were announced in 2002, hormone sales plummeted 30% to $1.9 billion, according to IMS Health, a health-care information company. Today, after subsequent analyses of the study and debates among specialists, it is getting clearer that the reported results is based on a misleading methodological bias, which led to a much too rapid generalisation.

The WHI data published in April 2007 by the Journal of the American Medical Association supports the concept that HRT has different effects on blood vessels in younger menopausal women (50 to 59 years old) than in women long after menopause. This study showed that women in their 50s who took a combination of oestrogen and progestin or oestrogen alone had a 30% lower risk of dying than women who did not take hormones (Mendelsohn and Karas, 2007 – table 7). Some of the methodological bias were, for instance, the high age of the participants, their health condition or their body-mass index; hence the reliability of the results are questioned and call for identifying clusters or sub-population profiles for which a given intervention is beneficial or at risk, especially with ageing persons. The HRT study is an example illustrating the challenge of designing studies to evaluate interventions whose efficacy is dependant on the complex clinical handling of each patient.

Table 7: Effect of Hormonal Use in Women > 50: latest findings 2007

1985:	A major study of nurses shows that those who use estrogens are 50% less likely to have heart attacks.
1991:	Women's Health Initiative (WHI) launched to study heart effects of hormones.
2002:	NIH stops the estrogen and progestin study, saying higher heart risks affect women of all ages. The estrogen-only study continues.
2003:	New England Journal of Medicine shows WHI women who started hormones within 10 years of menopause appeared to have 11% lower risk of heart attack.
2004:	NIH stops the second WHI hormone study that suggests oestrogen users have lower heart and breast cancer risk.
2006:	Archives of Internal Medicine reports 50 to 59 year old oestrogen users in WHI study appear to have 37% lower heart attack risk.
2007:	The most comprehensive analysis of the WHI shows 50 to 59 year old hormone users had a statistically significant 30% lower risk of dying compared to placebo group.

Source: WSJ Research

Timing Matters

How the risks of hormone use vary depending on the age a woman starts therapy compared to women who don't use hormones.

▼ Lower risk ▲ Higher risk

Age	Heart attack	Stroke	Death from any cause
50-59	7%▼	13%▲	30%▼*
60 to 69	2%▼	50%▲	5%▲
70 to 79	26%▲	21%▲	14%▲

*Statistically significant

Source: Jama April 2007

Although opinions may vary about whether the female menopause is a deficiency disease or a 'natural rite of passage', Crawford and Langhorne (2005) see several clear facts: "hormone replacement therapy can relieve some troublesome menopausal symptoms, but also has other important health effects, both bad and good. The Women's Health Initiative trial found that therapy did not meaningfully improve measures of physical and mental function or quality of life (Hays et al., 2004), but some effects that women might value—namely perceptions on youthfulness, attractiveness and skin tone—have not been adequately studied. Balancing these factors in individual treatment decisions can be difficult. […] In order to minimise these hazards, doctors should recommend hormone replacement therapy only for severe menopausal symptoms and for the shortest possible time in women who are fully informed of these risks. Despite the fact that there is no justification for regarding physiological menopause as a disease, it certainly marks the natural end of reproductive life and the advent of important metabolic changes."

The Women Health Initiative on Hormone Replacement Therapy: Methodological and Generalisation Bias in Risk vs. Benefit Analysis

"Last month, the New England Journal of Medicine reported that the 50-59 year-old women in the WHI who regularly used oestrogen alone showed a 60% lower risk of severe coronary artery calcium, an important risk factor for heart attack. How could the heart risks of menopause hormones for this crucial cohort change so dramatically in just five years? Officials from the National Institutes of Health, which directed the study of more than 27,000 women, say the interpretation of the WHI has simply evolved as researchers have used different methods to analyse the voluminous body of data. The average age of women in the study was 63. While older women in the study did show a heart attack risk, researchers eventually focused on women in their 50s who were closer to menopause, finding that hormones were more likely to protect those women's hearts than harm them. Critics, including some of the WHI's own investigators speaking out for the first time say that NIH officials initially over-generalised in large part because they excluded many of the study's own investigators and physicians from the first review. As a result, key questions that could have clarified the data far sooner were not asked.

Just 11 days before the public announcement in July 2002, the WHI's 40 investigators met in Chicago where they were told the study had been stopped early. Several people who attended the meeting reported that

> several WHI researchers were stunned and angry when they were given final page proofs of the study report for the Journal of the American Medical Association.[28] Although some researchers expressed concern that the results were too broadly interpreted, it was too late to make meaningful changes to the JAMA article. Many investigators who had spent nearly a decade working on the WHI had no input in the final and most important paper. Many in the medical community stress that the key questions about long-term use have not yet been answered. Although the WHI data clearly show that starting hormones at an older age is risky, what is unclear is whether the heart protection women get starting at a younger age will continue with long-term use. That was the question that the WHI was supposed to answer when it was launched in 1991 after data from an ongoing trial of nurses showed that women who used menopause hormones have as much as a 50% lower risk of heart attack. But the WHI designers did not take into account the fact that the timing of hormone use might affect the results and recruited mostly older, symptom-free women. Some of the study participants were already 20 years past menopause when the WHI began."
>
> (Wall Street Journal, 9 July 2007[29] – see also Mendelsohn and Karas, 2007)

Despite the recent data, questions about long-term use of hormones are far from resolved. The particular question that arises is whether hormones should be considered for heart protection together with blood pressure medications and cholesterol-lowering drugs called statins (see above). The National Heart, Lung and Blood Institute, which oversaw the WHI, believes that menopause hormones should not be used to prevent heart disease. "Long-term hormone therapy has these other adverse events hanging around. It doesn't fit the paradigm of what you are looking for in a viable long-term prevention strategy," says Dr Rossouw. "If you're going to use something to prevent atherosclerosis, your choice is statins, not hormones." The data on women who use statins are

[28] Rossouw J., Prentice R.L., Manson J.E., Wu L., Barad D., Barnabei V.M., et al. (2007): Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 297:1465–77.

[29] Tara Parker-Pope, "How NIH Misread Hormone Study in 2002", Wall Street Journal (USA), 9 July 2007:
http://online.wsj.com/public/article/SB118394176612760522.html?mod=blog

mixed, but suggest that they lower a woman's heart risk by 15% to 20% (Wall Street Journal, 9 July 2007).

Testosterone and HRT for women: A Cochrane systematic study reviewed the benefits of testosterone for peri- and postmenopausal women. The authors concluded that "there is evidence that adding testosterone to hormone therapy has a beneficial effect on sexual function in postmenopausal women. There was a reduction in HDL cholesterol associated with the addition of testosterone to the hormone therapy regimens. Due to lack of targeted research, it is difficult to estimate the effect of testosterone on sexual function in association with any individual hormone treatment regimen." (Somboonporn et al., 2005)

Conclusion: Hormone replacement therapy in women has risks and benefits. Controversies are still at hand on the balance between beneficial and deleterious effects, on the short-term vs. long-term effects and on the timing of the therapy and age of administration. Testosterone added to HRT show promising avenues for some conditions and should be further researched.

Continuous research and international scientific coordination of results are needed to keep up with the latest information for patients and consumers health. Clear guidelines for consumers and professionals are needed and should be promoted in all sectors (consumers, academics, websites, pharmacies, private practices, etc.)

5.5.4. Male Hormones: Testosterone Replacement Therapy

Background: Testosterone is a steroid hormone from the androgen group. It is primarily secreted in the testes of males and the ovaries of females, although small amounts are also secreted by the adrenal glands, and promotes the development and maintenance of male sex characteristics. It is the principal male sex hormone and an anabolic steroid. In both men and women, testosterone plays a key role in health and well-being as well as in sexual functioning. Examples include enhanced libido, increased energy, increased production of red blood cells and protection against osteoporosis.
Testosterone replacement therapy has been used successfully for years to treat men with abnormally low testosterone levels (hypogonadism). More recently, it is increasingly taken by healthy ageing men willing to boost testosterone levels,

yet not enough is known about the effects of testosterone therapy for this purpose. According to the Mayo Clinic, pharmacies in the United States filled 2.4 million testosterone prescriptions in 2004 which amounts to more than twice the number filled in 2000.[30] No data is available regarding the purpose of the use. In the absence of scientific evidence controversy is increasing regarding the need and effects of testosterone use. Testosterone replacement therapy can take the form of injectable depots, transdermal patches and gels, subcutaneous pellets and oral therapy.

For most men, testosterone levels decline after the age of 40 but still remain within the normal range causing no significant reported problems. Despite this fact, about two in 10 men aged 60 and older suffer from testosterone deficiency. As mentioned by Anderson et al. (2002), there has been a marked increase in testosterone prescriptions over the last few years. At present, most men receiving testosterone are between the ages of 40 and 65 years. With new products on the horizon such as patches, oral products (available all over the world) and nasal inhalators, the market is likely to grow exponentially over the next decade. There is a high probability that it will become a market of over $1 billion a year within the next 5 years. Most of the economic growth is expected to be drawn by male consumers aged 65 years and above.

Scientific evidence: While women's hormone replacement has been studied in detail, much less attention has been given to testosterone replacement in men. The difficulty to study testosterone levels, the lack of consensus on existing studies and the absence of large population surveys makes it difficult to conclude on any clear evidence that testosterone, and to a greater extent free or bio-available testosterone, declines with ageing (Feldman et al., 2002) or has specific proven and 'generalisable' effects. The clearest effect of testosterone replacement is on sexual behaviour: it improves libido and in some cases enhances the erectile function. Therefore, caution is given in reviews and one speaks rather of potential benefits and risks.

[30] www.mayoclinic.com

Table 8: Testosterone Replacement Therapy: Potential Benefits and Risks

Potential Benefits	Potential Risks
▪ Improves muscle mass and strength ▪ Increases bone mineral density ▪ Thickens body hair and skin ▪ Improves sexual desire ▪ Boosts energy ▪ Decreases irritability and depression ▪ Improves cognitive function	▪ Causes skin reactions ▪ Causes fluid retention ▪ Causes baldness ▪ Causes or aggravates sleep apnea ▪ Stimulates noncancerous (benign) growth of the prostate and causes or worsens urinary symptoms ▪ Stimulates growth of already present prostate cancer ▪ Enlarges breasts (gynecomastia) ▪ Stimulates growth of breast cancer that's already present ▪ Causes testicle shrinkage (testicular atrophy) ▪ Limits sperm production (infertility) ▪ Stimulates excess blood production ▪ Causes acne

Source: Mayo Clinic, 2006

Body and Performance enhancer: testosterone is often administered to athletes to improve performance—it is considered as a form of doping in most sports. Several easy-to-use methods exist including intramuscular injections, transdermal gels and patches, and implantable pellets. Anabolic steroids (of which testosterone is one) have also been taken to enhance muscle development, strength, or endurance—the muscle fibers increase and repair faster than in the general population. Despite the fact that the world of sports has proven the case of anabolic steroids and testosterone efficiency, very few studies currently exist to test the long-term effect of such intake, as well as its effects on the general population or on older men.

In older men, as Morley points out in his review, the major reason not to carry out a testosterone trial is the fear of side effects. Overall, the available data does not allow us to confidently predict the effects of testosterone on cardiovascular health, making it a prime target for a Men's Health Initiative endpoint (Morley, 2003; see also review of Haddad et al., 2007).

Some puzzling studies show however very different effects of testosterone levels. For example, that the level of testosterone in men may improve function and restore mental function given that punctual studies show that low testosterone levels may be associated with a higher risk of depression, of Alzheimer's disease, of falling in older men while high blood levels of testosterone after 50 years old is associated with increased cancer prostate risks. A recent study conducted by the University of Cambridge even showed that male traders in London make more money when their testosterone levels are high (see box below).

Testosterone predicts Profits on Trading Floors

A study lead by the University of Cambridge and reported in the Proceedings of the National Academy of Sciences demonstrated that male traders in the City of London financial district made bigger profits on days when their testosterone levels were already high: their daily testosterone was significantly higher on days when traders made more than their one-month daily average.

Researchers cautioned that testosterone may help focus the mind, but constantly high testosterone levels are likely to make traders foolhardy: the stress hormone cortisol seemed to be linked not with failure, but with uncertainty as reported by Dr John Coates, who led the study: "Rising levels of testosterone and cortisol prepare traders for taking risk. However, if testosterone reaches physiological limits, as it might during a market bubble, it can turn risk-taking into a form of addiction, while extreme cortisol during a crash can make traders shun risk altogether." The researchers believed they would find higher cortisol levels when the traders lost money, but this was not the case. Instead, cortisol levels rose during times of financial uncertainty. A team member, Joe Herbert of the Cambridge Centre for Brain Repair said: "Market traders, like some other occupations (such as air traffic controllers), work under extreme pressure and the consequences of the rapid decisions they have to make can have profound consequences for them, and for the market as a whole our work suggests that these decisions may be biased by emotional and hormonal factors that have not so far been considered in any detail." Coates, who is a former trader, said this may help explain both rational and irrational behavior. (Science News, Reuters, 14 April 2008[31])

[31] http://www.reuters.com/article/scienceNews/idUSN1440625120080414

Conclusion: Men face emotional and physical challenges as they get older. A decline in testosterone (below normal values) may justify taking supplementary testosterone. But it remains unclear whether restoring the testosterone levels to that of youth benefits older men or whether it may cause adverse effects. Thus the increased use of testosterone as an AAM product should be conducted under medical guidance and with caution.

5.5.5. Statins: Efficient to Reduce the Risks of Coronary Heart Disease

Background: Statins are considered as one of the medical and anti-ageing wonder drugs of the 21st century. They work by blocking a substance the body needs to produce cholesterol. They may also help the body to reabsorb cholesterol that has accumulated in plaques on the artery walls. Research findings also suggest that statins may have other potential benefits but doctors are still far from having all the information.[32]
The paradox of statins is that despite their proven efficiency, they remain in the sole hands of medical practitioners. Contrarily to other potential AAM products, statins have not reached the anti-ageing consumers and have not developed in manufactured products. If future effects prove that application to the larger public is safe, they may well become a targeted successful public health treatment.

Scientific evidence: The power of statins is well-known and its cholesterol-lowering effects are well documented. Statins or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (e.g. atorvastatin [Lipitor], simvastatin [Zocor]) are among the best-selling prescription drugs in the world and are widely viewed as very safe and effective (Golomb, 2004). Their benefits to coronary artery disease have been well-documented and are undeniable. In addition, statins have been shown to benefit survival in a large study of middle-aged men with heart disease or at high risk (Scandinavian Simvastatin Survival Study Group, 1994). These drugs block a substance in the liver needed to make cholesterol and help the body reabsorb cholesterol that has accumulated on artery walls, which reduces the risks of cardiovascular diseases. Other potential benefits are expected by researchers but need confirmation. This is the case of the anti-inflammatory properties of statins which can have effects on the brain and heart. Other benefits of statins include prevention of arthritis and bone fractures,

[32] http://www.mayoclinic.com/health/statins/CL00010

colon cancer, diminished risk of dementia and Alzheimer's disease. Statins also seem to have a neuroprotective effect. However, evidence suggests the balance between benefits and risks may be less favourable for the elderly and the metabolic balance may be affected negatively; with advanced age, cholesterol becomes a less reliable predictor of cardiovascular problems, and adverse reactions to drugs, including statins, may become more prominent such as muscle problems, diminished cognitive function, interaction with polymedication or body frailty (see review Golomb, 2004). While patients at high risk of cardiovascular disease receive mortality benefits from statins in studies on mostly middle-aged men (Scandinavian Simvastatin Survival Study Group, 1994), no survival benefit trend is observed in elderly patients who are at high risk for cardiovascular diseases (Shepherd et al., 2002). A less favourable risk-benefit profile may hold particularly for patients over 85, for whom benefits may be more attenuated and the risks more amplified (Weverling-Rijnsburger et al., 1997). In the 2002 Clinical Advisory on the Use and Safety of Statins, Pasternak et al. (2002) stressed the following factors as a potential risk for statin-associated myopathy: (i) advanced age (especially > 80 years, women > men), (ii) small body frame and frailty, (iii) multi-system disease, (iv) multiple medications, (v) perioperative periods, and (vi) concurrent use of certain medications. These factors are especially common among the elderly, which places them at increased risk for development of muscle problems with statins.

Conclusion: Clear and well-documented evidence exists on the beneficial effects of statins to reduce the risks of coronary heart disease and to lower cholesterol level. However, studies suggest that adverse effects might emerge in frail elderly or older people with specific health or pharmacological conditions.

Recommendations: There are reasons for concern that older people might cope less well with statins if not specifically selected for high cardiac risk or in frailer conditions than those generally involved in clinical trials. The case of statins portrays well the complexity of interventions in the elderly, especially with polymedication or suffering of polymorbidity: any time a patient with complex metabolic issues develops a new problem or worsens from an existing problem, the medication list should be reviewed with the new intervention, while keeping alert to the pharmacokinetics and pharmacodynamics of polymedication.

5.5.6. Chelation Therapy: Metabolic Cleansing

Background: Chelation therapy was developed during the 1950s as a way to cleanse the blood and blood vessel walls of toxins and minerals. Therapy involves infusions into the blood stream of the chemical edetic acid (EDTA). Sometimes the therapy may be administered by mouth with, occasionally, other chemicals. Chelation was initially used to treat heavy metal poisoning such as lead or mercury, but was often believed to be of benefit in other ways. In modern times, chelation practitioners may recommend this therapy for atherosclerosis (clogged arteries), heart disease, chronic kidney disease, peripheral vascular disease (claudication), diabetes, and many other health problems (up to 20 or more treatments). The term 'chelation' is also sometimes used in medicine as a general term to refer to the use of chemicals in the blood to remove specific toxins or contaminants (e.g. deferoxamine is a chelating agent used to treat excessive amounts of iron in the body) and should not be confused with EDTA chelation therapy. Although it has not been proven to be successful for heart disease, some doctors think that chelation therapy could benefit heart disease by binding to the calcium in the plaques clogging your arteries and sweeping it away.

(Source: Harvard Information Centre and Mayo Clinic)

Chelation therapy is extensively advertised and applied as an AAM treatment in clinics in Tokyo, Japan.

Chelation therapy is not new and was used by the British during World War II to treat victims of poison gas exposure. Its use was questioned for the cleansing of Plutonium and subsequent depleted Uranium in the military or for civilians exposed to weapons and bombs. An often-cited research on Uranium exposure conducted on Swiss mice showed that the length of time prior to initiating chelation therapy for acute uranium intoxication greatly influences the effectiveness of this therapy (Domingo et al., 1990). Today, chelation therapy remains the undisputed treatment-of-choice for acute lead poisoning, even in children, but a far more disputed choice for patients with atherosclerosis, a condition in which fatty substances build up in the inner walls of the arteries and clog them.

A Cochrane systematic review conducted on the effects of chelation therapy for people with atherosclerotic heart and circulation disease as a way of breaking down the blockages in their blood vessels. However, the review found that there is not

enough evidence from trials on the effects of this treatment (Villarruz et al., 2002). The Natural Standard Group[33] reviewed more than 10,300 articles on chelation therapy and concluded that while chelation may play a role in the treatment of lead or heavy metal toxicity, it needs the direct supervision of a qualified health care provider for any other condition (such as a treatment for clogged arteries or peripheral vascular disease). To date, studies are contradictory with either no significant effect, inconsistent results or with too few subjects. Adverse effects or even rare deaths (e.g. associated with hypocalcemia – MMWR, 2006) from chelation therapy have been observed and currently serve as a basis in different countries to recommend avoiding chelation for patients with heart, kidney, or liver disease, patients with conditions affecting blood cells or the immune system, pregnant or breast-feeding women, and children.

In the study conducted in Japan for this report, the situation was found to be very different: two renowned anti-ageing clinics in the Ginza centre of Tokyo promote and apply chelation therapy with equipment for several persons on a daily basis. Articles from Japanese scientific journals are rather laudatory about chelation therapy as an anti-oxidation therapy: "Anti-oxidation will be an important item in the 21st century to cope with ageing, heart attack, brain stroke, cancer, iatrogenic hazards, and environmental pollution involving human life. Chelation therapy will be a unique and necessary tool to scavenge oxidative stress" (Sajio and Hiroshi, 2000)[34]. The fact that parts of the population in Japan have suffered from radiation due to the atomic bomb and seek to eliminate potential presence of chemicals in the body could be an explanation for the wide use of this therapy in the country.

Conclusion: Given the potential risks and limited knowledge about the benefits of chelation therapy as a treatment for heart disease, many health authorities do not currently approve its practice, except in Japan.

Until more evidence is bought on specific applications, chelation therapy holds potential risks. Serious adverse effects remain for specific conditions and chelation should be avoided for patients with heart, kidney, or liver disease, patients with conditions affecting blood cells or the immune system, pregnant or breast-feeding women, and children.

[33] Natural Standard is an organisation in the U.S. that produces scientifically based reviews of complementary and alternative medicine (CAM) topics www.naturalstandard.com

[34] Posted on http://sciencelinks.jp/content/view/270/231/

5.5.7. Dietary Supplements

While classic medicine has for years largely minimised the importance of nutrition on health or as a therapeutic product, anti-ageing medicine has gone to the other extreme in the use of nutrition supplements and technology for prevention and treatment. For AAM, nutrition is revolutionised for boosting health and 'longevity' by systematically considering supplementation and micronutrients targeted to combat age-related ailments. A selection of the major dietary supplements will be presented to clarify their efficiency and risk and accordingly make recommendations concerning their medical use or public consumption.

a. Folic Acid

Background: Folic acid is a B-vitamin, which guarantees cell growth. If taken before and during early pregnancy from a multi-vitamin or from fortified foods, folic acid can prevent some forms of birth defects, especially spina bifidia. Today, it is prescribed not only for pregnant women but advertised and applied for anti-ageing purposes.

It is difficult, though possible, to obtain the recommended dosage of folic acid through ordinary food habits, the human body actually absorbs the synthetic form of folic acid better than its natural form called 'folate'. Therefore in 1998, the U.S. Food and Drug Administration required the addition of folic acid to foods such as enriched breads, cereals, flours, pastas, and rice in order to increase the amount of synthetic folic acid in the general population's diet. In addition, most experts recommend that women of childbearing age should take 400 micrograms of synthetic folic acid daily, from fortified foods and/or a daily multi-vitamin as well as eating a variety of foods as part of a healthy diet. As indicated in the box below, major U.S. campaigns were organised to promote folic acid.

Two Major U.S. Campaigns for Folic Acid

All women, every day!?: As a woman, you need folic acid every day, whether you are planning to get pregnant or not, for the healthy new cells your body makes daily. Think about your skin, hair, and nails. These—and other parts of your body—make new cells each day.

You might think that you can get all the folic acid and other vitamins you need from the food you eat. But it is hard to follow a diet that has all the daily nutrients you need. Even with careful planning you might not get all the vitamins you need from your diet alone. Hence, the importance of taking a vitamin with folic acid every day. Today's women are busy! They know the importance of exercise, of good diet and of sufficient sleep and they wonder how they can fit in one more thing every day, so a few seconds to take a vitamin pill is easy and offers all the folic acid needed.

Fact Card for Adolescents: The U.S. Centers for Disease and Prevention Control (CDC) have been working hard to fulfil your requests for a folic acid educational material for an adolescent audience. The new fact card, entitled 'B Your Best with Folic Acid,' has been developed and tested with young students in grades 5 to 8.

(U.S. Centers for Disease and Prevention Control, 2007[35])

b. Antioxidants and Antioxidant Vitamins

Background: Oxidation is a natural process that leads to cell and tissue damage. Antioxidants are substances that slow this process and can be found naturally but also in many available supplements. Although antioxidants have some health-promoting properties, it is not clear if antioxidant supplements offer the same benefits as food. Antioxidants are frequently used by anti-ageing consumers.

The potential beneficial effects of antioxidants in protecting against disease have been used as an argument for recommending increased intakes of several nutrients above those derived by conventional methods. If it is possible to quantify such claims, antioxidant properties should be considered in decisions concerning the daily necessary intake of these nutrients. The Mayo Clinic states that much research has been carried out to evaluate the potential role of antioxidant supplements in preventing heart disease with no conclusive evidence. Some studies even suggest that antioxidant supplements—which contain antioxidants at levels thousands of times higher than those in food sources—have harmful effects.

[35] http://www.cdc.gov/ncbddd/folicacid/women.htm

For example, people who take more than 400 international units of vitamin E a day may be at increased risk of death. For these reasons, the American Heart Association does not recommend routine use of antioxidant supplements to prevent or treat cardiovascular disease. It supports a diet that is high in food sources containing antioxidants (table 9) and other heart-protecting nutrients, such as fruits, vegetables, whole grains and nuts, to reduce the risk of cardiovascular disease.

Table 9: Food Sources of Antioxidants

Good food sources of antioxidants	
Type of antioxidant	**Foods**
Beta carotene	Sweet potatoes, carrots, squash, cantaloupe, pumpkins, apricots, mangos, collard greens, spinach and kale
Lycopene	Tomatoes and tomato products
Vitamin A	Liver, sweet potatoes, carrots, milk, egg yolks and mozzarella cheese
Vitamin C	Oranges, tangerines, broccoli, grapefruit, green peppers, strawberries and tomatoes
Vitamin E	Almonds, wheat germ oil, safflower oil, corn oil, soybean oil, mangos, nuts and broccoli

Source: Mayo Clinic, 2005

Antioxidant Vitamin E Supplements – The Case of High-Dose Response Risk: According to Butler et al. (2002), some epidemiological studies have suggested that dietary supplementation with vitamin E reduces the risk of cancer (Heinonen et al., 1998), and cardiovascular disease (Knekt et al., 1994). Butler et al. however underline that such observations are not universal. According to McCall and Frei (1999) except for supplement vitamin E, and possibly vitamin C being able to significantly lower lipid oxidative damage in both smokers and non-smokers, the current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans. On the basis that vitamin E reduces oxidative stress, clinical trials have flourished to test its efficacy in preventing various chronic diseases. A few meta-analyses have shown no overall effect of vitamin E on survival (Vivekananthan et al., 2003; Shekelle et al., 2004; Eidelman, 2004). A recent meta-analysis added a

missing component to former studies by evaluating the potential dose-dependent effect of vitamin E supplements and found a statistically significant correlation between dosage and response: all-cause mortality increased with a high-dosage of vitamin E supplements (> 400 IU/d) (Miller et al., 2005). Given the consistent findings on high-dosage vitamin E supplementation, policymaking bodies should caution the public against the use of high-dosage vitamin E supplementation. Despite the need of more controlled clinical trials to evaluate safety of high-dosage vitamins, guidelines have however recommend the use of vitamin E supplementation in disease-specific situation such as for patients with Alzheimer's disease to delay it's progression (e.g. Doody et al., 2001).

In view of the increased mortality associated with high dosages of beta-carotene (Vivekananthan et al., 2003) and now vitamin E, use of any high-dosage vitamin supplements should be an important public health concern. Antioxidants supplements should not be recommended for use by the general population to reduce the risk of cardiovascular diseases as current guidelines have stated (e.g. Kris-Etherton et al., 2004); others, such as from the American Cancer Society are more moderate: "High doses of supplements may also slow the way the body absorbs vitamins A, D, and K, and result in deficiencies of these vitamins. Megadoses of vitamin E supplements are not advised for people who are taking blood-thinning drugs, such as warfarin, because the supplements might counteract the effects of the drugs. People with cancer should talk to their doctor before taking vitamin E or other vitamin supplements, especially while they are undergoing chemotherapy or radiation therapy." (Source: http://www.cancer.org)

On the other hand, in 2003 the European Commission's Scientific Committee on Food, in their opinion document on the 'Tolerable Upper Intake Level of Vitamin E', took a moderate position. The fact that vitamin E deficiency can cause a proliferative vasculopathy in premature neonatal infants, and a number of neuropathological disturbances, cardiomyopathy, and haematological disorders in children and adults, should also make us aware of the important benefits of vitamin E in supplementing in specific cases.
AAM controversy should in no way hinder or become an obstacle to access the right substance in case of deficiency for those who need it most. Care should be brought to methodological factors such as gender, age, and health condition in any meta-analysis or systematic review addressing antioxidants and antioxidant vitamins.[36]

[36] http://ec.europa.eu/food/fs/sc/scf/out195_en.pdf

c. Functional and Fortified Food for the Population: From Brain to Neutraceuticals, Cosmeceuticals or Nutritional Genomics

Background: Biotechnology is making a significant impact on food production with great potential for responding to population needs. However, there are currently no clear international and national regulations on the boom created by the 'modified food industry' as it falls under agriculture regulation and not under the stricter rules on health and medication regulation in most countries.
New fields using dietary and specialty supplements are proliferating and expanding with new terms such as functional food, fortified food, designed food, bio-tech food or techno-food. While some innovative supplemented foods could be of benefit to public health, such as iodine supplementation in the form of iodized salt or oil, others could have irreversible long-term consequences not only for individuals but for the community (e.g. genetically modified food).

Biotechnological food is more in the realm of manufacturers, most of their products are based on the concept of adding pharmacological substances to daily nutrition, and even changing the agriculture system in order to sell a new type of food, 'enhanced food' supposed to boost the health and well-being of the population. This blending of food and medication is also called 'neutraceuticals' (see section below) reflects the commercialisation and popularisation of medication as an element of nutrition and sold in supermarkets beside 'natural food'. This trend is on the rise: joint ventures between the food industry and the top academic institutions are proliferating such as in the case in Switzerland a signed agreement between Nestlé and the Swiss Federal Institute of Technology in Lausanne (EPFL) to develop 'Brain Food' (see box).

Nestlé and EPFL sign a research partnership for 'Brain Food' development

As part of an effort to understand better the relationship between what we eat and how we think, EPFL signed a five-year agreement with Nestlé research to study nutrition and the brain. The *Nestlé* Research Centre (NRC) and EPFL (one of the two Swiss Federal Institutes of Technology) signed a five-year agreement to conduct research on the relationship between nutrition and the brain.

Under this agreement, *Nestlé* will contribute CHF 5 million per year to research at EPFL's Brain Mind Institute, where two Nestlé Chairs will be established. The research will extend from studying the role nutrition plays

> in children's brain development to identifying ways of slowing down brain decline in older age and preventing diseases such as Alzheimer's. The agreement will also include research into taste perception and flavour enhancement.
>
> (EPFL News, 28.11.2006[37])

Nutraceuticals *(word merging nutrition + pharmaceutical):* Many food products sold on the market today could be called nutraceuticals or fortified foods such as salt with iodine or fluorine, which has had an important impact on public health and reduction of related diseases (e.g. goitre and caries). According to the Oxford dictionary 'nutraceutical' is a term for compounds in foods that are not nutrients but have (potential) therapeutic effects, and is also called functional food. A consensus was reached to define nutraceuticals "*as dietary supplements delivering a presumed bioactive agent derived from food sources, but in a non-food matrix at concentrations far higher than could feasibly be obtained from the food source, and which is used for specific health-enhancing effects*." The definition is broad enough to encompass an astonishingly wide variety of substances ranging from familiar antioxidant vitamins to animal products like shark cartilage or bovine colostrum. Besides providing the definition, a task force of the American Association of Clinical Endocrinologists (2003) has provided practical guidelines for the use of 'nutraceuticals' and other dietary supplements out of concern for the many bioactive substances included. Those substances delivered without prescription are for example synthetic hormones and hormonal supplements which have potential endocrine effects. A thorough list of bioactive substance can be found on their website such as coenzyme Q10, flavonoids, isoflavones and ipriflavone, phytosterols, saw palmetto, glutamine, taurine, carnitine, creatine, chondroitin, glucosamine, omega-3 fatty acids including fish oils, probiotics, dehydroepiandrosterone Sulfate (DHEAS), androstenedione.[38]

Cosmeceuticals *(word merging cosmetics + pharmaceutical)*: According to the U.S. Food and Drug Administration (FDA), a cosmeceutical is a term used by the cosmetic industry to refer to cosmetic products that have medicinal or drug-like benefits. The typical product of cosmeceuticals would be an 'anti-ageing

[37] http://actualites.epfl.ch

[38] See website full report or listing summary:
http://www.aace.com/pub/pdf/guidelines/Nutraceuticals2003.pdf
http://www.guideline.gov/summary/summary.aspx?doc_id=4265&nbr=3265

cream' or 'collagen powder' to add to your morning breakfast. The word is new and not recognised by federal institutions in the United States such as the FDA or the Food, Drug and Cosmetic Act, which insists that they "do not recognise any such category as 'cosmeceuticals'. A product can be a drug, a cosmetic, or a combination of both, but the term 'cosmeceutical' has no meaning under the law". While cosmetics are defined by their intended use, as articles intended "to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body […] for cleansing, beautifying, promoting attractiveness, or altering the appearance", the FDA states that the "Food, Drug and Cosmetic Act defines drugs as those products that cure, treat, mitigate or prevent disease or that affect the structure or function of the human body. While drugs are subject to an intensive review and approval process by FDA, cosmetics are not approved by FDA prior to sale. If a product has drug properties, it must be approved as a drug."[39]

Nutritional Genomics: Nutritional genomics is the specific application of genomics in research pertaining to agriculture and food consumption. During the last ten years, more knowledge on the bioactive effect of specific substances is known and constitutes one of the basis of what is called *'functional food'*. The concern of the food industry today focuses on tailored functional foods and personalised foods for specific needs (e.g. anti-ageing bioactive yoghurts and teas). In this context, genomics research is arousing hope that food will be adaptable to individuals' genetic profiles and susceptibility to disease ranging from intestinal cancer to food infection. Genomics research is helping to map these phenomena and give personal 'food advice' adapted to individual genetic constitution. Consumers will be choosing food on the basis of their own genetic constitution.

Genetically Modified Food: The biotech developments are driving forces well beyond nutraceuticals and cosmeceuticals. Closer to nutritional genomics, the trend toward manufacturing genetically modified foods and other agricultural biotechnology products has generated significant public debate. The potential for creating foods enhanced for health benefits or increasing crop yields was tantalising, but there was also widespread concern about the technology's health and environmental risks. The Pew Initiative on Food and Biotechnology spotlighted policy issues arising from these discussions (box below).

[39] See: "Is It a Cosmetic, a Drug, or Both? (or Is It Soap?)", FDA, 2002: http://www.cfsan.fda.gov/~dms/cos-218.html

From fortified to modified food, world citizens are concerned with the proliferation of biotechnological food in their daily shopping and want to know what they buy, eat and what are the effects of the food we currently eat, as has very clearly shown the global threat of avian flue or mad cow disease (i.e. Bovine Spongiform Encephalopathy). Therefore, the international scientific community continues to assess and challenge biotechnology's role in improving the food supply and call for stronger regulation and safety measures from governments and multinationals. As long as safety guarantees are not acceptable, public debate will certainly continue worldwide (see box).

Public Wants Biotech Food Tested:
Individual Self-Regulation is Not Enough …

Most people in the U.S. believe the FDA should verify whether a genetically modified food is safe before consumers eat it, according to the Pew Initiative study which found that 89% of the people interviewed believe that genetically modified foods should not be allowed on the market until they are proven safe. The study found that although up to 75% of processed foods in grocery stores contain genetically altered foods, only 24% of Americans believe they have eaten them and 58% say they have not. According to the Pew Initiative,[40] almost 100 million acres of crops in the United States are genetically modified.

In reality, however, the agency does not independently test genetically modified foods for safety. A federal law passed in 1992 states that genetically altered foods are the same as any other food, and they therefore do not require FDA review and approval. The 1992 law states that biologically engineered foods, which contain DNA from other organisms, are no different and pose no greater safety concerns than any other food. Therefore the safety process is very simple: before putting genetically modified foods on the market, biotech executives simply submit a summary of their data declaring the product to be safe and the FDA returns a letter acknowledging it. For example, in 2002 the famous Montsanto firm submitted a summary of his own study on a new genetically altered corn which was immediately approved on the basis that the results presented "did not raise issues that would require pre-market review or approval by FDA."

[40] http://www.pewtrusts.org/our_work_detail.aspx?id=442

Activists are not the only ones concerned. The General Accounting Office said in a 2002 report[41] that the FDA's oversight of genetically modified foods could be enhanced. Critics like Cummins and Hansen believe genetically engineered foods could be harmful to human health and should be regulated at least as stringently as new food additives, which undergo thorough FDA testing and review as mandated by the federal Food, Drug and Cosmetic Act.[42]

(Wired, 19.9.2003[43])

Recommendations: The emergence of 'artificially supplemented food' poses serious problems of regulation as they do not fall under the drug regulation but under agriculture regulation. Therefore blending nutrition with pharmaceutics certainly holds great risks for consumers who are unaware of the potential short- and long-term of their food consumption.

Before more research demonstrates the safety of this new type of 'food', any food which has been modified at the farming level as well as manufactured level should be carefully labelled with risks and 'unknown data'. This would avoid statements on products with false claims or false safety of its generic drug properties. Any claims made regarding the product must be substantiated by scientific evidence as truthful with a clear label indicating the 'safety level' or risks for vulnerable populations. New regulatory monitoring systems that bridge this confusing gap between scientific claims and marketing deceptions for the population should be clarified at the international level, as well as better coordinated in the European region.

5.6. External Interventions

Innovative technological developments have taken place in the last decades which have opened new doors on external ways to counter some undesirable effects of ageing; the promises range from enhancing beauty to replacing or extending artificially lost functions, to environmental robotic life support systems. The most spectacular progresses for the image we hold of ageing

[41] http://www.gao.gov/new.items/d02566.pdf
[42] http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm
[43] http://www.wired.com/medtech/health/news/2003/09/60501

concern external interventions on the body. Technological aesthetic medicine is now susceptible to modify the look, enhance the body and thus fight superficial effects of ageing (e.g. anti-ageing plastic surgery, Botox, laser resurfacing, or body sculpting). Some promising technological developments aimed at restoring the loss of limb/functions from life-long or acquired handicaps and impairment are today being applied with increasing success to all age groups. Without being exhaustive, we will review some of the current technological developments used or applied to improve ageing conditions or reverse lost function and mobility.

5.6.1. Aesthetic Interventions: Face-Body Rejuvenationation

a. Botox – *Botulinum toxin* Type A

Background: Botulinum Toxin Type A (Botox Cosmetic) is a protein complex produced by the bacterium Clostridium botulinum.[44] It is injected in the body and is effective in weakening or paralyzing certain muscles or in blocking certain nerves. The effects last about three to four months. Side effects can include pain at the injection site, flu-like symptoms, headaches and stomach upsets. First introduced in the 1980s, botulinum toxin has since proven its efficiency with little or no side effects. Its use has increased due to the fact that doctors applied it to an increasing number of medical conditions.

(U.S. National Library of Medicine)

Botox injections are the fastest growing cosmetic procedure in the industry, according to the American Society for Aesthetic Plastic Surgery (ASAPS). In 2001, more than 1.6 million people received injections, an increase of 46% over the previous year. More popular than breast enhancement surgery and a potential blockbuster, botox is regarded by some as the ultimate fountain of youth and has even created a new trend among some groups who organise ‘botox parties’.

Botulinum toxin has been used efficiently in clinic practice for a range of applications. It is used as a treatment for ailments such as migraine headaches, cervical dystonia, blepharospasm (involuntary contraction of the eye muscles),

[44] FDA definition and statistics: http://www.fda.gov/fdac/features/2002/402_botox.html

severe primary axillary hyperhidrosis (excessive sweating), or for other conditions more disputed, such as overactive bladder syndrome with or without incontinence, anal fissure, spastic disorders associated with injury or disease of the central nervous system, etc. Meta-analyses assessing the risks of botulinum toxin type A (BTX-A) across all common therapeutic indications demonstrated that the formulation of BTX-A is safe and has a favourable safety and tolerability profile across a broad spectrum of therapeutic uses (Naumann and Jankovic, 2004).

Besides the proven benefits, botulinum toxin is not without risks: it is considered as potentially 'poisonous' and may lead to serious conditions if wrongly administered. The point that the Journal of American Medical Association (JAMA) published the conclusion of the Working Group on Civilian Biodefense that developed consensus-based recommendations for measures to be taken by medical and public health professionals against botulinum toxin if it is used as a biological weapon against a civilian population (Arnon et al., 2001; Working Group on Civilian Biodefense, 2001; Kortepeter and Parker, 1999[45]).

The cosmetic form of botulinum toxin, often referred to by its product name Botox®, is a popular non-surgical injection that temporarily reduces or eliminates frown lines, forehead creases, crows feet near the eyes, and thick bands in the neck. The toxin blocks the nerve impulses, temporarily paralysing the muscles that cause wrinkles while giving the skin a smoother, more refreshed appearance. Studies have also suggested that Botox is effective in relieving migraine headaches, excessive sweating, and muscle spasms in the neck and eyes (American Society of Plastic Surgeons[46]). Today, Botox is not only widely known, but is becoming more accessible to all at different prices and in various ways according to country regulations. Botox injection consumers presently concern the largest part of society (various ages, social positions, etc.). The price range goes from CHF 300 to 1,000 per treatment in clinics located in the French part of Switzerland (Forever Laser Institute, Geneva; Centre New Line, Geneva; La Clinique, Montreux; Concept Esthetic, Paudex) depending on the surface and site (estimate Tribune le Matin, 28.7.2007).

[45] Kortepeter and Parker report for CDC (Centre for Disease Control) on potential biological weapons threats:
http://www.cdc.gov/ncidod/EID/vol5no4/kortepeter.htm

[46] http://www.plasticsurgery.org/patients_consumers/procedures/Botox.cfm

In July 2007 a UK clothing catalogue, Grattan, offered customers a range of non-surgical procedures such as Botox. The British Association of Aesthetic Plastic Surgeons reacted promptly with serious concern that 'off-the-shelf' sales undermined the seriousness of the procedures: "It is essential the public understand that aesthetic procedures, even if they are non-surgical, are not commodities to buy off-the-shelf and cannot later be exchanged for a different style or size." The company responded that consumers received a consultation and were fully informed before undergoing any procedure (BBC News, 8 July 2007). The trend is international and sooner or later the same problem will arise in all parts of Europe, which calls for preventive measures to improve safety for the consumer. To help consumers who consider a Botox injection, the American Society for Dermatologic Surgery provides a safety check list (see box below).

Considering Botox Cosmetic?

- Be sure that a qualified doctor performs the procedure.
- Make sure that the doctor is trained and qualified in cosmetic skin surgery of the face.
- Ask questions and be informed about the benefits and risks involved in the procedure.
- Avoid alcohol and remain upright for several hours following the procedure.
- Choose a medical setting using sterile techniques. Necessary equipment should be available to respond to any potential problems.

(The American Society for Dermatologic Surgery[47])

Today new products emerge which could erode the market supremacy of Botox. These products are proven to be more efficient, less invasive and at lower risk. For example, the Swiss Technology Award 2006 gave its prestigious prize for a new anti-wrinkle cream with better and longer lasting effects than Botox (see box).

[47] http://www.asds.net

Better Than Botox?
SYN®-AKE, a new anti-wrinkle active compound from snake venom
Swiss Technology Award 2006

PENTAPHARM[48] has won the Swiss Technology Award 2006 with its new active ingredient SYN®-AKE. SYN®-AKE is a new anti-wrinkle active compound based on a synthetic tripeptide that mimics the effect of Waglerin-1 a peptide that is found in the venom of the Temple Viper, Tropidolaemus wagleri.

In-vitro tests have shown that SYN®-AKE significantly reduces the frequency of contraction of innervated muscle cells as a function of the incubation time. Waglerin-1, a protein contained in the venom of the snake Tropidolaemus wagleri, has the property of blocking neuromuscular contraction. Following extensive wide screening, the development of a synthetic peptide that mimics the activity of the selected protein has been made possible. SYN®-AKE is offered as a glycerine-based aqueous solution. In-vivo tests show the excellent anti-wrinkle effect of SYN®-AKE. SYN®-AKE has been thoroughly tested and is considered to be appropriate for cosmetic applications.

PENTAPHARM has developed, during the past 30 years, a unique approach to the breeding and housing of venomous snakes and particularly the Brazilian Lance Adder, Bothrops moojeni, whose venom is used for therapeutic (anticoagulants, haemostatics) and diagnostic products. Currently, some 10,000 specimens of this snake species are bred and housed at PENTAPHARM DO BRASIL, making PENTAPHARM the largest snake breeder and keeper in the world.

(http://www.biovalley.com/dn_biovalley_news/pentapharm060116.html)

Conclusion: Botulinum toxin, known as Botox, is a drug, not a cosmetic. However, people from all social classes request Botox injection. As it is effective (for a few months), there is a foreseeable increase in much younger and much older generations, under 18 and over 65 years, although it has not yet been tested thoroughly. Products such as SYN®-AKE are developing into creams which are more efficient, less invasive, with longer effects and lower risks.

[48] www.pentapharm.com

Recommendations: There is a general misunderstanding that anything that can be used for cosmetic purposes must be easy to use and safe. But just like many other AAM interventions or cosmetic surgery, professional training is needed. Given the risks, restriction of Botox administration to medical doctors should be maintained or a very strict certification put in place for potential business practices. Safety evidence is urgently needed in the use of Botox for younger and older age groups as consumers are increasing in both groups. One could add that Botox has created a socio-cultural phenomenon, which beside the potential economic deprivation, the emergence of a psychological addiction to Botox or similar products would not be of surprise in the future. This factor should not be forgotten when designing preventive measures or new regulations like for any other drug easily leading to addiction by European and Swiss public health agencies (in Switzerland: Swiss Office of Public Health and Medical cantonal offices).

More information on non invasive and safer anti-wrinkle technologies such as SYN®-AKE should be encouraged.

b. Mesotherapy: The New Cellulite Treatment

Background: Mesotherapy, a variety of minimally invasive techniques in which medications are directly injected into the skin and underlying tissue in order to improve musculo-skeletal, neurological, and cosmetic conditions. It is widely used in anti-ageing medicine. Mesotherapy injections are supposed to target fat cells by inducing rupture and cell death among adipocytes. Beside laser techniques, mesotherapy is a cosmetic procedure promoted especially for cellulite treatment, liposculpting, and body contouring.

Mesotherapy treatments have been performed throughout Europe, South America, and more recently the United States for over 50 years. However, physicians have been concerned about both the efficacy and safety of mesotherapy, arguing that a lack of scientific study makes mesotherapy a fad with potentially dangerous side effects. “There is simply no data, no science and no information, to my knowledge, that mesotherapy works”, according to Rod Rohrich, chairman of the department of plastic surgery at the University of Texas.[49] The American Society of Plastic Surgeons issued a position statement urging not to endorse mesotherapy because to date, no established mechanism of action demonstrated efficacy or established safety profile with any of the drugs used in mesotherapy.

[49] http://www.hughesdermatology.com/wiki/PHD/Mesotherapy

Conclusion: In the context of the often cited obesity pandemic, mesotherapy is appealing to the consumer and many health practitioners are adopting it. Too little evidence currently exists on the efficacy of mesotherapy in all its forms, whether through medical practices or substances used.

Ethical problem: A simple injection is giving people false hopes. Everyone is looking for a quick fix but currently there is no 'quick fix' for fat or fat deposits or for cellulite; on the other hand, neither the substance injected nor the price are thoroughly controlled so that financial abuse for false hopes could be legally questioned. Furthermore, it is difficult to make any claims after such therapies, as failure could easily be attributed, though impossible to prove, to other factors (e.g. eating habits, genetic patterns, environmental factors).

c. Resurfacing and Therapy with Technological Devices: Laser, Intense Pulsed Light (IPL), Radiofrequency (RF) and others

Background: Technological devices serving AAM, especially cosmetic corrective surgical procedures in medical and private practices, are developing at an unprecedented pace all around the world. Describing such therapies and treatments using devices such as lasers, Intense Pulse Light (IPL), or Radiofrequency (RF) resurfacing is complex with technical information that is hard to decipher. Those treatments are also often presented on websites by physician companies and/or aesthetic institutes, private practices, or wellness centres with claims and promises that the patient/client not only cannot verify but which are often misleading. Cosmetic resurfacing procedures can be performed with many reliable techniques and instruments exist.
Non-ablative treatments target the lower layers of skin (dermis), while leaving the skin's surface (epidermis) intact. Ablative laser resurfacing targets both the surface and the lower layers of skin by injuring or 'ablating' the surface of the skin. Lasers can perform either ablative or non-ablative resurfacing, while IPL and radio frequency resurfacing are considered non-ablative methods. The system you choose depends on the results you are looking for and the degree risk you are willing to take.[50]

[50] For review with different description of devices with scientific sources see:

Since the mid-90s, ever more sophisticated technological machines have emerged to treat skin and facial modifications, either age-related or for aesthetic reasons. Beside laser, different devices such as flash lamps, Intense Pulsed Light (IPL), Radiofrequency (RF), and infrared light are among the most common tools for facial resurfacing and rejuvenation. The use of the new generations of machines requires a precise and accurate diagnosis of the surface to treat to avoid irreversible and even fatal consequences. Although safe and well-used devices are known and applied by trained physicians, a high risk persists in the use of high-tech machines by non-medical practitioners with neither official training nor required expertise.

For this reason, enforcement to control non-medical practice or create a specific certificate to allow the use of sophisticated technological devices in private practices and businesses would be needed in Switzerland and in Europe. In spite of the enforcement of the new Swiss legislation in 2004 (ODim, art.18, annex 6), many cases of victims have been reported (while many go unreported) by the Swiss Society of Dermatology and Venereology (SSDV).[51] Governmental action is needed, as consumers feel too often ashamed to take juridical action to bring the practitioner to court. Thus, not only is there a need for legislation but also for an efficient and open reporting system with lawyers who are able to respond and take further action in the framework of the new jurisprudence.

The fact that international devices are sold directly to medical and non-medical practitioners without thorough control or knowledge about the risks and consequences of new technological devices (e.g. laser) is also a matter of high concern. A serious survey should be urgently conducted among the 3 parties interacting around those fast developing technological devices:

http://www.paulaschoice.com.au/learn/article.asp?PAGETYPE=ART&REFER=SKIN&ID=19 or for example, the description of the different clinical applications on the site of a dermatologist in Switzerland: www.skinpulse.ch

[51] http://www.derma.ch and http://www.bag.admin.ch/suchen/index.html?keywords=laser

(i) The technology marketer
(ii) The technology user (practitioners)
(iii) The patient/consumer

In 2005, the SSDV issued a position statement warning against the non-medical use of the Intense Pulse Light Systems (IPLS): Variable Pulsed Light, Controlled Pulsed Light, Intense Flash Light, and flash lamps (SSDV Bulletin, 2005[52]). After detailed description of laser therapy and IPL system treatments as well as the risks involved, they request better safety for the sake of the patient and consumer, based on the following requirements:

(i) that indication treatment of IPLS for pigmentation alteration can only be performed by a medical doctor specialised in dermatology;
(ii) that treatment by IPLS remain reserved to medical doctors specialised in dermatology;
(iii) that any users of IPL systems are required to be certified by a specialised education;
(iv) that professionals going into IPLS treatment or laser technology be required to take part in continuous and regular education in this field.

Conclusion: While treatment with specialised medical doctors using new technological devices such as laser therapy, flash lamps, Intense Pulse Light (IPL) or Radiofrequency (RF) is safe, its use by non-specialised or non-medical practioners with no specific training holds high risks for the patient's safety.

Recommendations: Given the evidence of the increasing number of complaints and undetected cases, the above described position statement from the Swiss Society of Dermatology and Venereology should be followed and implemented in Switzerland.

Ethical issues: The policy system on cosmetic technological device is today 'abuse-friendly' and urgently needs a case reporting system to address malpractice, misuses, and abuses at the medical and financial level.

[52] www.derma.ch

d. Chemical Peel

Background: Chemical Peel uses a chemical solution to improve and smooth the texture of the facial skin by removing its damaged outer layers. Although chemical peel may be performed in conjunction with a facelift, it is not a substitute for such surgery nor will it prevent or reverse the ageing process. Chemical peel is most commonly performed for cosmetic reasons—to enhance appearance and self-confidence. It may also remove pre-cancerous skin growths, soften acne facial scars, and even control acne.
Risks: All chemical peels carry some uncertainty and risk. Chemical peel is normally a safe procedure when it is performed by a qualified and experienced dermatologist or a plastic surgeon and enhances aesthetic appearance.

e. Multiple Interventions with Plastic/Aesthetic Surgery

AAM external interventions can be multiple and with visible results or failures. Dr Katsuya Takasu, one of Japan's most famous celebrity plastic surgeons, during his interview for this report, made a point that plastic/aesthetic surgery and external interventions were the safest existing AAM interventions with nearly zero risks. To prove this to his patients, Dr Takasu even went to the rare extreme to perform surgery on himself demonstrating his own rejuvenating process and displaying bluntly a clear reversal of his 'appearance age' through different methods (surgery, resurfacing, hair transplant). The contrasting evidence is visual, he looked his age of 65 a few years ago and today he looks 20–25 years younger! He himself declares: "Today I not only look, but most importantly feel like I was 45 years only." To build upon evidence and credibility, Dr Takasu filmed the anti-ageing interventions and underwent local anaesthesia in order to direct himself the surgery procedures. The video film of his transformation, an unquestionable marketing tool, is publicly displayed on his website with videos and clips of his various interventions.

Auto-Transformation: Dr Katsuya Takasu Self-Rejuvenation Process[53]

'Low cost' plastic surgery and outsourcing market: As with mobile phones, technologies which a few years ago were unaffordable for low and middle class are getting more and more accessible and at cheaper prices. The democratisation of plastic surgery is one of those technologies. Today, access to a wider range of consumers is growing through 'low cost offers' of all types. For example, the 'Easy Look' clinic in downtown Geneva[54] is offering a much lower price for minimum catering and overnights in a clinic with accredited medical surgeons using the facilities of the clinic. The 'Easy Look' concept was created, on one hand to respond to the need of the population with less financial capacity, and, on the other hand, to decrease medical tourism to less developed countries with higher risks of uncovered post-operative complications. The Swiss low cost clinic is expanding now in different European countries with local surgeons. The typical client profile seeking a low price aesthetic or anti-ageing surgery or procedures is young to middle-aged and motivated to invest in beauty. In a context of strong consumer demands, the offers all-inclusive cheap holidays including 'plastic surgery shopping' and 'wellness clinics' is blossoming in many developing countries, creating a flourishing business. AAM has readily started to 'outsource' its market to foreign countries with an uncontrollable scope.

[53] http://katsuya.takasu.co.jp/movie/index.html
[54] www.easylook.ch

In Lausanne, a service named 'Label Esthétique' organises aesthetic interventions and vacation at advantageous rates in Tunisia, in Lyon, or in Paris. Advertisement on the website proposes directly online registration for a first medical pre-surgery check-up: "We organise an all inclusive travel from Switzerland (Lausanne) for medical and aesthetic surgery patients".[55] A much wider range of interventions are offered as less costly package deals in luxury hotels in places like Tunisia compared to France or Switzerland where the interventions are ambulatory and restricted to different formats of lifting or liposuction.

5.6.2. Human Enhancement: 'Pushing It All To The Limits'

The current and promising applications of biotechnology has brought a new face to medicine with 'enhancement'. Many authors underline the difficulty, impossibility, or futility of any definition that seeks to distinguish enhancement from therapy (Juengst, 1998; Parens, 1998). Despite the polemic, the term 'Enhancement' has not found any viable substitute. The problem raised by Pellegrino (2004)[56] is that no boundary between morally valid and invalid uses of biotechnology can be established without at least a working definition. However, the definition of enhancement can be grounded in its general etymological meaning, i.e. to increase, intensify, raise, exalt, heighten, or magnify. This definition applied to humans can take many forms, either at the physiological level (e.g. genetic manipulation, cybernetics, nanotechnology, or psychopharmacology), or at the macrobiological level through body parts replacement (e.g. titan prosthesis, engineered articulation, or brain chips), as a prolongation of the body (e.g. bionic skin, night vision enhancement devices, bioengineered limbs, exosqueleton), or as an environmental device to replace functional restrictions (e.g. robots and smart houses, remote control solutions). This new technology at the service of human function has led to very passionate ethical debates on the potential abuse or deviation in the evolution of mankind onto a trans-human species or post-human era. Anti-ageing medicine promotes the use of human enhancement for reaching its ultimate goal, a life-long peak performance of the body and the mind-but does not promote excesses. Besides the ethical debate that will be treated later in the report, we will present a few interesting and promising developments for potentially improving the quality of life of the ageing population.

[55] "Nous organisons un séjour en 'all inclusive' pour les patients en médecine et chirurgie esthétique", see: http://www.labelesthetique.com

[56] Centre for Bioethics and Human Dignity, see: http:/www.cbhd.org/resources/biotech/pellegrino_2004-11-30.htm

a. Bionic Body: From Arms to Body Suits

Medical science has made significant progress with prosthetic artificial replacements of 'used' body parts, allowing many patients to restore and maintain their mobility and independent living. Subsequently, such medical technologies have also significantly contributed to longer and healthier lives. Technological progress in biomaterials continues to bring substantial improvement to the lives of chronologically ageing individuals: for example in the area of prosthesis and artificial body parts replacement or in the field of bioengineered tissues. Prosthetic devices have now taken a new turn with advances in engineering, generating and compensating for loss of strength and energy: this trend sits today under the name of 'bionic' arm, legs, and more body parts or exosqueletons performing what the body can no longer perform.

The new findings presented below illustrate the societal revolution those progresses bring: on one hand it gives hope to people who lost a limb (see illustration below: case of Maryland bionic arm), or those who lack strength (see illustration on bionic suit for the elderly), on the other hand it also raises serious ethical issues (see box on military use of engineered bionic bodies).

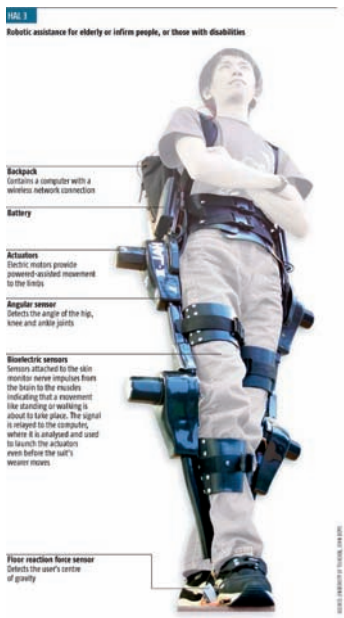
"Bionic arms turn science fiction to fact"
(Washington, Sept. 2006)

Ms Mitchell, from Maryland in the US, is the fourth person, and the first woman, to receive a 'bionic' arm that allows her to control parts of the device by thought alone. Designed by physicians and engineers at the Rehabilitation Institute of Chicago, the bionic arm device works by using the brain's ghost memory of the missing limb, translating commands to move muscles in the missing limb to movements in the bionic arm.

Bionic Suit or Exosqueleton Developed in Japan: the Robotic Assistance for the Elderly, Disabled or Infirm People

A ROBOT suit has been developed that could help older people or those with disabilities to walk or lift heavy objects. Dubbed HAL, or hybrid assistive limb, it is the result of 10 years' work by Yoshiyuki Sankai of the University of Tsukuba in Japan, and integrates mechanics, electronics, bionics, and robotics in a new field known as cybernics. This 'bionic suit' gives the wearer super strength and is said to solve many of the functional impairments of ageing. Sankai has had many requests for the devices from people with brain and spinal injuries, so he is planning to extend the suit's applications to include medical rehabilitation. The first commercial suits are likely to cost between 1.5 and 2 million yen ($14,000 to $19,000) and were promised to be made available in the U.S. for purchase by the end of 2005 for less than $19,000. The robotic exoskeleton boosts muscle power for both the legs and arms, enabling you to lift some 40 kilograms more than you otherwise could and fight crime.

(Source: New Scientist, 9 April 2005)



The 'orthopedic' bionic body, once science fiction, is now routine. Surgery is conducted on a growing number of older people and at higher ages. New joints with new materials are today replacing used bones and joints: "New York's Hospital for Special Surgery replaces more than 4,000 joints every year. It's not uncommon that we have patients who have multiple replacements. They will have both hips and knees replaced and also a shoulder replacement", says Dr Thomas Sculco,[57] Hospital's Surgeon-in-Chief. More so, anesthesia and operations are safer and recovery time reduced for very old people. Worn out joints are today replaced, not only for older people as new materials allow for balls and sockets that last for decades.

Is 'The Super Elderly' a Myth or the Next Generation of Bionics?
"The Vanderbilt Arm", an Example of Military Application

A rocket-powered bionic arm has been successfully developed and tested by a team of mechanical engineers at Vanderbilt University as part of a $30 million federal military programme to develop advanced prosthetic devices for next generations of super soldiers. The mechanical light arm prototype with a miniature rocket motor can lift (curl) about 20 to 25 pounds, three to four times more than current commercial arms, and can do so three to four times faster. "That means it has about 10 times as much power as other arms despite the fact that the design hasn't been optimised yet for strength or power," Michael Goldfarb, the professor of mechanical engineering who is leading the effort, said. Conventional prosthetic arms have only two joints, the elbow and claw, but the prototype's wrist twists and bends and its fingers and thumb open and close independently. The Vanderbilt arm is the most unconventional of three prosthetic arms under development by the Defense Advanced Research Project Agency (DARPA) programme. The other two are being designed by researchers at the Advanced Physics Laboratory at Johns Hopkins University in Baltimore, who heads the programme. Those arms are powered by batteries and electric motors. The programme is also supporting teams of neuroscientists at the University of Utah, California Institute of Technology and the Rehabilitation Institute of Chicago who are developing advanced methods for controlling the arms by connecting them to nerves in the users' bodies or brains.

(http://www.vanderbilt.edu/exploration/stories/bionicarm.html)

[57] NBC News 11 December 2003: "Bionic body now a reality, Joint replacement not just for the elderly" by Robert Basell – http://www.msnbc.msn.com/id/3541566/

The question could be asked as to why the bionic arm, bionic suit and other bionic devices would be part of human enhancement. Just looking at the 'palliative' side of restoring a lost function with bionic devices replacing body parts is not enough. The development of the next generation of bionic prostheses is already there. The U.S. military is very keen, not only on restoring the members of their military soldiers who lost a body part in the last Irak war, but they see in bionic body parts an opportunity to enhance performances of the soldiers beyond the 'natural' body capacity, creating a species of 'super soldiers' for the field. In this perspective, the idea of strength and muscular decline with age could find a surrogate which could make adepts in the population. The ethical issue here is how far the human race can legitimately modify the 'natural capacity' of their bodies with unnatural means, enhancing unequal artificial power which can be harmful, and for what purpose.

b. Robots and Humanoid Robots: Caregivers and Support for the Elderly's Daily Living Activities

Japan holds the world record number and proportion of centenarians. With the shortage of caregivers in a country with an immigration rate near zero, policymakers are wondering who will care for their parents. The development of robots has been one of the solutions proposed by the Japanese Government to care of the elderly. A number of different prototypes have entered the market and claim to be sold widely. Technological progress of robotic solutions is constantly moving ahead which explains that former 'star robots' disappear to prepare for new generation of robots. This was the case for our report seeking to visit *Sony* to see the famous robotic pet "Aibo" (see picture below).

This section will briefly cover a selection of the current Japanese robotic market. In 2003, *Mitsubishi* announces the scientific creation of a robot named "Wakamaru" which they claim has the potential to replace a human caretaker and could be used in the homes of elderly Japanese who have no one to look after them.

In 2003, Wired News published the picture of Wakamuru, a 3-foot-tall frame robot, which contains an integrated cell phone programmed to call emergency dispatchers automatically if a problem occurs with a patient. An embedded web camera lets doctors and family members keep an eye on the patient at all times. Speech-recognition software and a built-in dictionary provide the robot's vocabulary. Wakamaru is so robust that he or she—*Mitsubishi* can give the robot either a male or female voice—can be programmed to remind patients to take their medicine and even call a doctor when it appears that someone is in distress. While Wakamaru may frighten people who are not used to being around robots—it resembles a science fiction alien more than a human child. In Japan, robots are much more acceptable members of society. "Japan, on the one hand, has this social-political issue," said Mark Tilton, a professor of Asian politics at Purdue University. "It is also a place where robotics has been the most developed." (Source: Wired News, "Wakamaru Bot at Your Service", Elisa Batista, 04.24.03)

Robotic Life Support Partners for the Elderly

In 2005, *Toshiba Corporation* launched a robotic 'life support partner' for the elderly and for children, which distinguishes particular voices among many voices or sounds from multiple directions. The robot can also interact with the speakers by responding to a repertoire of instructions: "A sophisticated robot able to deliver human-centric technologies that provide assistance and support to the elderly and

young children in the home and in such public places as shopping complexes." (Source: Internet Journal of Emerging Technologies – MedGadget, 1 June 2005: "ApriAlpha™, ApriAttenda: Home Life Support Robots") Those life supports are also developing into furry pets: "Paro", who won the Japanese Robotic Award. It is designed primarily to be a 'furry friend' with health benefits: it is meant to simulate the soothing and cardioprotective benefits of pet ownership. The furry robot's surface has tactual sensors mimicking the human body which reacts to elderly's touch. Approximately 800 bodies are already used in Japan and scheduled to be sold outside the country (Source: MedGaget/geriatrics 2006).

Robotic pets with soothing and cardioprotective benefits

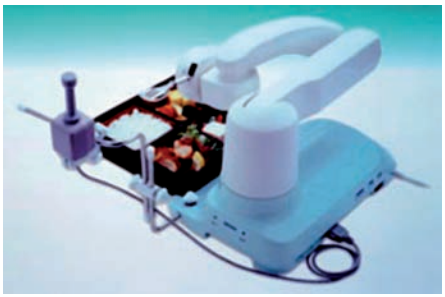
"ApriAlpha"
the Life Partner

"Paro"
the 'furry friend' for the old

Activities of Daily Living Robotic Supporters

Robots or robot-like technologies are developing rapidly to the point that they are today aiming at replacing caregivers and daily routine work such as feeding older persons with serious mental or physical impairments. Another 2006 award winning medical gadget was developed in Japan which aims at facilitating eating with different degrees of robotic mechanisms to bring food to the mouth (see below). By operating a joystick on a tray, the user can eat different types of food such as porridge, rice or salads. It also adjusts to the condition of the user with 3 operation modes (manual operation, semi-automatic and automatic). It is sold in Japan but also in European countries such as the Netherlands (Source: MedGadget/geriatrics 2006).

Robotic Help for Eating by Operating a Joystick, 2006 Japanese Award



Toyota is on the development race for robots and is focusing on humanoid robots as "partner robots" for other activities of daily living. *Toyota* is promoting the development of three different types of partner robots (walking, rolling, and mountable, see on next page), each with its own areas of expertise. *Toyota* strives to develop the most 'human' robot possible with positive human characteristics such as being agile, warm, and kind and also intelligent enough to skillfully operate a variety of devices in the areas of personal assistance, care for the elderly, manufacturing, and mobility. Furthermore, since each area requires a special set of skills, the following is an overview of the partner robots announced by Toyota (source: www.robotmatrix.org).

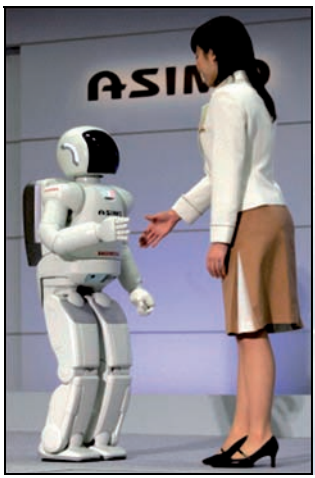
Different Models of Humanoid Robots for Daily Living

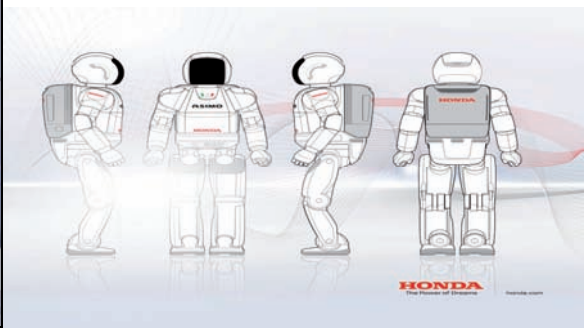
Walking Model walks on two legs similar to a person. It is an assistance robot designed to help the elderly.

Rolling Model zooms along quickly without taking up much space. Its mobility makes the robot suitable for manufacturing activities.

Mountable Model capable of carrying its passengers almost anywhere they need to go.

A Promising Robot: ASIMO





ASIMO BIODATA
Advanced Step in Innovative Mobility
www.asimo.honda.com
130 centimetres tall and weighs 54 kilograms

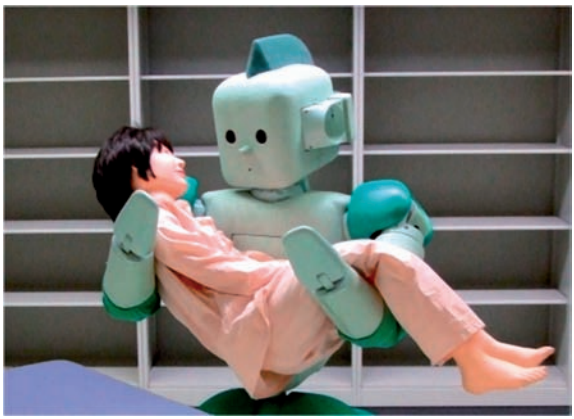
Honda engineers began developing a humanoid robot in 1986 for the purpose of someday helping people in need. After years of research and development, they created an advanced humanoid robot able to function in real-world environments. In 2002, ASIMO was presented when it rang the opening bell at the New York Stock Exchange. The latest version of ASIMO was launched in 2007: new features such as flexibility, ability to run up to 6 km/h, give hope that in a not-too-distant future humanoid robots will assist humans in their homes. Many applications can be expected from ASIMO, of which certain are in function such as:
Security Teacher: "Step to Safety with ASIMO", a pedestrian safety program that teaches children safe ways to cross the street. This DVD video program is available free of charge to educators, police officers and safety advocates across the nation through ASIMO's website.
Orchestra Conductor: ASIMO performed "Impossible Dream" to open a special concert performance with renowned cellist Yo-Yo Ma on May 13, 2008 by conducting the Detroit Symphony Orchestra for young people.
To see Asimo run click http://world.honda.com/HDTV/ASIMO/New-ASIMO-run-6kmh/

Conclusion and recommendations: Japanese technological development is unique, it is meant not only to respond to the challenges of their ageing population but to find new age-friendly robotic solutions for a robotic-friendly culture. Robots in Japan are developing at a fast pace with fascinating prototypes such as the latest "Asimo" which can only leave us perplex in front of a new perspective on a 'robotic enhanced quality of life for the old'. Reality joins science-fiction with prototypes which most would think unimaginable.

Beside the large array of Smart Housing technologies already existing in various countries to facilitate living and ageing at home, advances in robotic solutions coupled with progresses in microchips and wireless systems will enable more and more sophistication in electronic-robotic monitoring. Integrating robotic humanoids or mimicking humans for nursing, caring, cleaning, transporting, leisure activities could revolutionise daily living. Nursing homes today could also take advantage of new technologies to improve the quality of life of their residents with electronic security, automated doors, remote control monitoring and much more. Even small devices can make a difference. More information and technological strategies for the elderly should indeed be developed and transferred to targeted institutions.

The Japanese expansion in robotic and bioengineered technology is rich in innovative solutions for an ageing population and a source of inspiration for national policies.

Robotic "Caregiver for the Elderly"



c. Robotics for Rehabilitation and Locomotion Therapy

Disability and functional incapacity is one of the conditions which affects the individual's quality of life and often precipitates the person in a gradual loss of mobility. Today's research demonstrates that even at higher ages, rehabilitation through mental and physical training has an impact and is important in restoring the loss of function. Functional movement and sensory stimulation play an important role in the rehabilitation of neurological patients following stroke, spinal cord injury, traumatic brain injury, as well as in patients with multiple sclerosis, Parkinson's disease or other neurological diseases and injuries. The concept of 'task-specific learning' based on neuroplasticity suggests that activities of daily living may be trained and improved through numerous repetitions and intensive training.

The rehabilitation robotics field in Europe, although technically well advanced, is penetrating the market very slowly and is still seen to be 'future technologies'. A main reason is the availability of alternative solutions but other factors limit the potential market success. Potential users as well as most rehabilitation advisors do not know the potential capabilities of robots or are unaware of the existence of rehabilitation robots. As underlined by an EU report more than 10 years ago,[58] the decision to purchase a rehabilitation robot is influenced mainly by the expected value of the solution. This can only be estimated roughly by hours of independence gained by its usage, or expressed in perceived utility, or in perceived costs saving. Reimbursing organisations are usually not familiar with this kind of new technology, and therefore they are not convinced of the benefits.

However, recent rehabilitation technologies have been developed and tested with unprecedented success giving hope to a flourishing market. Those solutions are based on robotic exosqueleton and are about to completely modify the way we so far envisioned rehabilitation and even walking for people with frailty or handicaps. Solutions such as the Lokomat system (see box below) have been studied, tested and are currently used in hospitals and homes, boosting the rehabilitation process at an accelerated rhythm with results beyond expectations. Lokomat replaces 2 physiotherapists with more efficiency for movement control, thus more efficient results for the patient.

[58] Bühler Christian, "Robotics for Rehabilitation: Factors for Success from a European Perspective": http://www.asel.udel.edu/robotics/newsletter/sprsum97/europe.html

Lokomat® System Robotic Exoskeleton
Restoring Function through Engineered Therapy

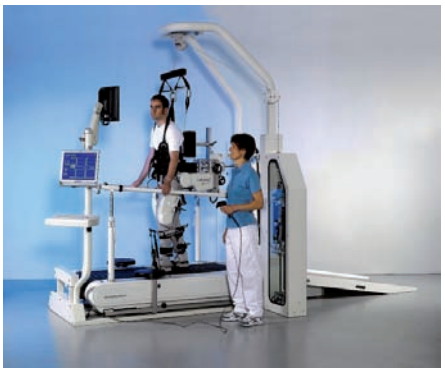
Swiss Technology Award 2006

Hocoma is considered a leader in robotic rehabilitation therapy for neurological movement disorders and is committed to support clinicians and patients in neurorehabilitation with innovative, high-quality therapy solutions. It was granted the Swiss Technology Award in 2006 for one of their products which is continually being improved: the Lokomat® System robotic exoskeleton. It is currently tested as a gait rehabilitation aid for individuals with spinal cord injury and stroke. The Lokomat is the world's first driven gait orthosis that automates locomotion therapy on a treadmill and improves the efficiency of treadmill training.

Advantages of Lokomat based therapy:

- A driven robotic gait orthosis guides the patient's legs on a treadmill offering a wide range of training possibilities;
- Physical strain on therapists is relieved, single operator mode;
- Patient walking activity is easily monitored and assessed;
- Improved motivation through visualised performance feedback;
- Gait pattern and guidance force are individually adjustable to the patient's needs.

Neurological patients with movement disorders caused by stroke, spinal cord injury, traumatic brain injury, multiple sclerosis or other neurological diseases and injuries as well as small children with cerebral palsy can profit from our therapy solutions.



(http://www.hocoma.ch/web/en/header/index.html)

5.6.3. Viagra: The Case of a Risky Consumer-Driven Market

Background: Erectile dysfunction is most prevalent at advanced ages and impinges on the quality of life of men and women.
No treatment has shown to be efficient before Viagra (Sildenafil citrate) was tested, developed and approved by U.S. FDA in 1998. Rapidly, Viagra gained reputation all over the world and was adopted in particular by anti-ageing consumers, often without taking their sexual health condition into account.
Viagra is the first oral pill to treat impotence, a dysfunction that affects millions of men. Viagra is manufactured by *Pfizer Pharmaceuticals*.

The popular interest in Viagra is largely due to media coverage, and the fact that the demand for treatment rapidly increased in the whole world has made it the fastest selling drug. According to *Pfizer Pharmaceuticals*, sales amounted to $1 billion during the first year of production. The demand is being met by prescription in the United States and globally through the internet and on the street, which in Europe preceded its licensing for prescription by doctors. No precise data is available on the profile of Viagra clients (e.g. age, socio-economic position, motives).

Scientific evidence: Viagra treatment has been evaluated in numerous trials and studies. At least 69 related deaths were observed from March to July 1998 during which 3.6 million prescriptions were dispensed. However, the FDA took no regulatory action (FDA, 1998).[59]

Sildenafil was also adopted as an enhancer of sexual performance by men, even by some women without sexual dysfunction—sometimes in combination with stimulants. It shows clearly how easy it is for consumers to make inappropriate use or misuse when information on safety or dependency is still lacking. Alternatively, research has demonstrated that consuming Viagra puts older persons at higher risks, especially with given health conditions.

[59] See Cornell University review of Viagra history:
http://wo-pub2.med.cornell.edu/cgi-bin/WebObjects/PublicA.woa/2/wa/viewHContent?website=wmc+medicine&contentID=732&wosid=Frg6Suu3p0tHJM8gCC9gS0

From Lawsuits to an Update on Product Labelling

Information sheets for consumers and professionals were issued in 1998, and revised in July 2007 by FDA, after fatal outcomes or lawsuits for subsequent medical problems came to light due to Viagra intake. A small number of men have lost their sight in one eye some time after taking Viagra. FDA has therefore imposed new labelling for Viagra to include information on possible eyesight loss (NAION). People who have a higher probability for NAION include those who suffer from heart disease or diabetes, are over 50 years, have high blood pressure, high cholesterol levels, smoke, or suffer from certain eye complaints.[60]

Recommendations: The case of Viagra shows that monitoring case reports, federal legislation (information to consumers, to professionals, labelling) in collaboration with researchers is imperative. For consumers' safety, efficient information and reporting system must be put in place at the federal level in coherence with international regulations. Continuous research must be conducted to examine its effectiveness and safety in long-term use and in patient groups so far excluded from previous studies or those that are most vulnerable. Viagra raises other interesting questions concerning cases who would benefit more from curative treatments such as surgery or other therapies then Viagra. Such alternative treatments can contribute to determine the differential impact of a successful treatment on long-term quality of life as well as on mental and physical health.

5.6.4 Case Study: AAM and Technological Progresses in Opthalmology

By Dr Kaweh Mansouri, ophtalmologist

In this section, two of the most promising areas are identified that could open new scientific vision for the next decade.

[60] http://www.fda.gov/cder/consumerinfo/viagra/

a. Eye-Disease and Dietary Supplements

Red Wine and eye disease prevention: Alcohol has been part of the human civilisation for 6,000 years, serving both dietary and socio-religious functions. As recently as the 19th century, alcoholic beverages were relatively dilute and were considered superior to water since they were less associated with illness and provided at the same time important caloric intake and other nutrients. Until recently, however, most attention was dedicated to the adverse health effects of alcohol. Obisean and co-workers were the first to show the protective effect of moderate wine consumption and reduced risk of developing Age-Related Macular Degeneration AMD (Obisesan, 1998). These findings were supported by subsequent studies that adjusted for confounding variables. It is likely that more than one mechanism is involved in the protective effect of wine on the macula of the eye. These include the anti-inflammatory, antioxidant and antiplatelet properties of wine. These compounds are found in higher concentrations in red than in white wine. The right amount of wine that is beneficial is unknown. There are significant variations between studies of the association between wine consumption and AMD. The variance appears to be related to a lack of information on the exact amount of wine ingestion that is beneficial in reducing the risk of AMD. Most studies on the association between wine and AMD to date either do not have the sample size or on wine consumption required to provide clear-cut recommendations.

Glaucoma and Omega3: A recent study by Nguyen and co-workers suggests protective effects of omega-3 fatty acids in glaucoma (Nguyen et al., 2007).[61] It shows that increasing dietary omega-3 fatty acids can reduce IOP with age because of increased outflow facility and could therefore play a role in the dietary planning. Their study was, however, conducted on a rat population and warrants confirmation in humans.

Cataract and Vitamin Intake: Vitamin intake seems to play a role in the development of cataracts. A recent study analysed data from 3,000 people and showed that incidence of cataracts was 60% lower in those who had taken a supplement of multivitamins on a daily basis for 10 years or longer (Mares-Perlman, 2000). There is also some evidence on the role of statins in cataract formation. Klein and co-workers could show a lower incidence of nuclear

[61] Nguyen C.T., Buy B.V., Sinclair A.J., Vingrys A.J. (2007): Dietary omega-3 fatty acids decrease intraocular pressure with age by increasing aqueous outflow. Invest Ophtalmol Vis Sci, 48(2):756–74.

cataract in patients under long-term statin intake (Klein et al., 2006). However, currently, few reliable data exist and several large-scale clinical trials to establish a clear relationship between dietary intake and incidence of cataracts are under way.

Neuroprotection (Memantine): Neuroprotection, a strategy to slow or prevent the death of retinal ganglion cells, offers the possibility of slowing the rate of glaucomatous progression and preventing blindness. It targets the final common pathway of retinal ganglion cell injury and is aimed at blocking primary destructive events or enhancing the survival functions of the retinal ganglion cells and their axons (Hare et al., 2004a, 2004b). Neuroprotection has been studied for therapeutic application in various conditions, such as Alzheimer's disease and stroke. Studying its potential benefit in glaucoma therapy is difficult because disease progression is a very slow process and trials would require a long follow-up and large number of participants.
Numerous mechanisms are implicated in neurodegeneration leading to glaucomatous vision loss. One of the most abundant neurotransmitters is glutamate, which can be toxic if present in excess. One of the potential candidates to block glutamate is Memantine hydrochloride, a moderate affinity NMDA-receptor antagonist. It has been used in Parkinson's disease for over 20 years. Up to this day, only animal model studies are available in which the substance has shown to prevent neuronal degeneration. Currently, a multicentre clinical trial is underway, with promising intermediate results.
Given the current dynamic in research in this field, there is well-funded hope, that over the next decade, neuroprotective agents will likely become available to clinicians and bring about a paradigm change in the way glaucoma patients are treated.

b. Cosmetic Interventions for the Ageing Eye

Botulimum toxin: Botulinum toxin is an exotoxin produced by the bacterium Clostridium botulinum. It is considered to be the most potent biological toxin in nature. Since its introduction into clinical medicine three decades ago, it has become a major therapeutic drug with applications in various medical subspecialities, spearheaded by its use in ophthalmology. It has been applied in wide range of ophthalmic disorders, such as dystonic movement disorders, eyelid retraction, lacrymal hypersecretion, nystagmus, strabismus, and oscillopsia.

In recent years, the use of botulinum toxin in aesthetical medicine, especially in anti-ageing therapy has gained increasing popularity (Klein, 2004; Flynn, 2003). Initially, the treatment of facial wrinkles with botulinum toxin focused on the reduction of dynamic wrinkles. Off-label applications have now expanded to the treatment of many other areas of the face and include 'crow's feet' and 'smoker's lines'. Side effects are mostly transient and benign.

c. Genetic Testing

Genetic testing for inherited eye diseases is one of the most promising areas in ophthalmology. Contrary to popular belief, the concept of genetic testing is not a recent phenomenon although these were not DNA-based; for decades numerous genetic tests have been performed to screen patients for genetic diseases, such as tests for inborn malfunctions of metabolism, sickle-cell anaemia, or an electroretinogramme for retinopathies. Milestone endeavours such as the Human Genome Project and the HapMap Project have since created a much clearer topography of the human genetic landscape.

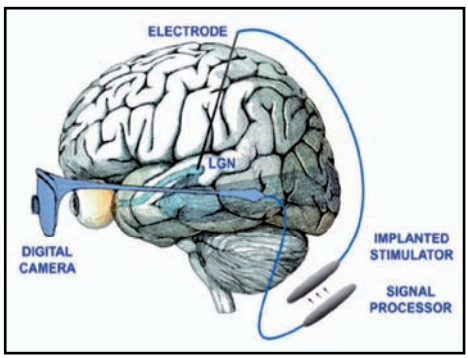
Ophthalmology has a long history in the field of genetics and is today at the forefront of tackling the problems of more complex diseases. Indeed, the first inherited disease in which the chromosomal location was identified was X-linked colour blindness. Genetic eye diseases widely range in prevalence from common disorders such as glaucoma and age-related macular degeneration, which affect 10–30% of people over the age of 70 years, to less common conditions. Faced with the 3 billion nucleotides of the human genome, the current genetic diagnostic tools for complex diseases are still in their infancy. However, our understanding of the genes involved in inherited ophthalmic diseases has improved greatly. The possibility that deployment of efficient genetic testing for common eye diseases can become widely available within 5–10 years could revolutionise the way clinical ophthalmology is practiced. At the dawn of the genomic era, efforts should be made to prepare clinicians on the translation of this new information into practice.

d. Artificial Retina (Retinal Chips, "Bionic Eye")

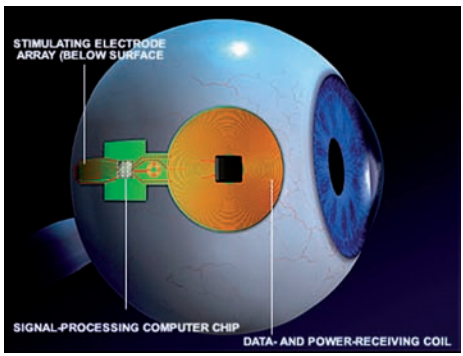
For decades, the possibility of restoring sight to blind individuals has been a subject of intense scientific research. New hopes have been generated by recent advances in microfabrication technologies, neuroscience, biomaterials, and information technologies leading to the development of highly sophisticated neural prosthetic devices designated to interact with the nervous system.

Numerous retinal chip studies are underway in different centres. Most of these studies are investigating the optimal location of the chip within the eye as well as the chip's long-term viability and compatibility with surrounding tissue. Most artificial retinas are being designed to replace lost photoreceptors and other retinal tissue. The artificial devices are designed to convert light into visual information and send them back to the brain via the optic nerve. One of the leading teams involved in the development of artificial retinas, under Prof. Humayun at the University of Southern California, has recently started a second generation, FDA-approved clinical trials of bionic retina—modelled after the cochlear implant—that could restore sight to people who have gone blind as a result of the most common progressive eye diseases. Their system uses a spectacled-mounted camera to feed visual information to an array of 60 electrodes in the retina. So far, six patients who had lost vision as a result of retinitis pigmentosa have benefited from this device.

The development and realisation of devices for visual neurorehabilitation are more complex than auditory devices and require extraordinary diverse and lengthy collaboration among basic scientists, engineers, and clinicians. Several studies have highlighted that following the loss of vision, the brain undergoes profound neuroplastic transformation and that the occipital cortex is a major site of these changes. The understanding of these changes will be essential in developing visual prosthetic devices.



Research opens way for a "bionic eye" that could potentially restore sight (BBC world 2007)



Boston Retinal Implant Project (The Boston Globe, 5 December 2004)

Note that some alternative solutions are offered to restore eye strain or fatigue have been proposed in other cultures such as vision therapy, also known as eye exercise, vision training, or orthoptics. In the Indian culture it is known as "Yoga of the Eyes" on the basis that exercises can help to strengthen the eye muscles (http://www.visiontherapy.org).

Permanent Lens Implants:
Revolutionary Technology for Recovering Optimal Vision

Permanent lens implant procedures are developing at a fast pace. Here are two examples, severe nearsightedness and biofocal lens implant, although new multifocal lens implants for other eye problems are today offered in many clinics.[62]

Severe Nearsightedness (2005)[63]

Eyesight in people who have severe nearsightedness and face a dearth of treatments can now undergo surgery to implant a permanent lens. Ophthalmologist Scott MacRae, M.D., director of the Strong Vision Refractive Surgery Centre at the University of Rochester Eye Institute in New York witnesses the rapidity of today's technological progress: "This surgery produces one of the most dramatic improvements in quality of life that I have seen in my 20 years as a corneal surgeon," says MacRae. "These are patients who really are blind without glasses. If they knock their glasses off the nightstand, they're blind—for many, their greatest fear is to be caught in a situation like a fire in a hotel where they could lose their glasses and not be able to find their way out."
The surgery offers an option between life-long thick glasses or contact lenses to patients legally blind. In studies of the device, 84% of patients with vision 20/400 or worse, improved to at least 20/40.The key to the new procedure is a plastic lens that is implanted permanently into a person's eye to correct the person's abnormal vision. The lens is implanted just behind the cornea and in front of the iris and the eye's natural lens during an outpatient procedure that lasts about an hour. It is the first time the FDA has approved (2005) a permanently implanted lens to correct nearsightedness.

[62] U.S.: http://www.eye-care-center-albany.com/cataract-surgery-multifocal-lens-implants.html
UK: http://www.eye-care.org.uk/item_view.php?item_id=269&content_id=6

[63] New Technology an Option for Severe Nearsightedness, University of Rochester News (January 2005) – http://www.urmc.rochester.edu/pr/news/story.cfm?id=715

Bifocal Lens Implant (2007)[64]

Anyone who wears reading glasses or bifocals can report on its inconvenience. Yet there is a bifocal lens implant that may get rid of your reading glasses for the rest of your life.
A permanent bifocal lens recently approved by the FDA can improve both near and far vision. It is called ReSTOR® lens, and it uses technology similar to those used in microscopes to help the eye distribute the proper amount of light without relying on eye muscles which weaken with age. After the eye is numbed with drops, a tiny incision is made, and the natural lens is emulsified and removed. The ReSTOR® lens is inserted in its place. The patient is awake during the procedure, which takes about 20 minutes. The procedure costs about $1,000. Medicare covers part of the bill, and patients must pay the difference in cost over conventional lenses.

5.6.5. Technologies for Repairing, Enhancing and Restoring Function

Technological aids where developed at first to compensate for a loss of function and for sensory deficit, two brief examples:

a. Hearing Loss and Auditory Devices

Whether a person worked in a loud factory, played in a rock'n'roll band or mowed lawns for a living, associated noises can easily be the cause of hearing loss. Today, the next generation of auditory devices based on the traditional hearing aids not only palliates the hearing loss, but compensates, monitors sounds, and has even improved in 'beauty' and 'camouflage strategies'.

Just to mention here the phenomenal progresses made in auditory devices which from being noisy, uncomfortable and visible have become tuned, self-monitored, with zooming sound function and are smaller and less visible than ever before. Hearing aids come in many special colours to match your skin, hair, and bright colours for kids even. With today's advances in hearing aid devices, it is possible to get a digital hearing aid; this device will do automatically adjustments to the sound levels. Many rock'n'roll stars are interviewed on TV wearing hearing aids, only visible to the alert watcher.

[64] Bifocal Lens Implant May Replace Reading Glasses, NBC5, Chicago TV (February 2007) – http://www.nbc5.com/vision/11096193/detail.html

Prototypes of a bionic hearing device are being tested but currently no conclusive application is available.

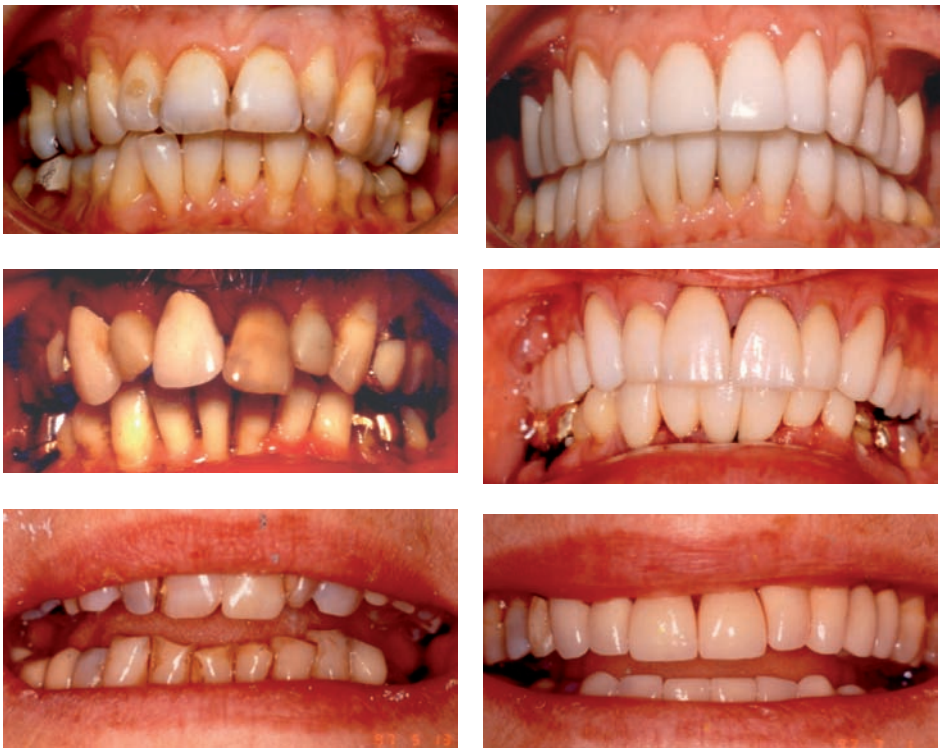
b. Cosmetic Dentistry

Teeth are important for quality of life, they are an essential 'instrument' to keep the choice to eat all types of food and find enjoyment. Healthy teeth and mouth are also important factors in social and sexual life, being able to smile, feel attractive and comfortable with a partner. AAM has captured its central feature in combating ageing, and restoring a young smile and healthy look. Dentistry is no longer just a case of filling and extracting teeth, as it had been for many years. Nowadays, many people turn to cosmetic dentistry or 'aesthetic dentistry' as a way of improving their appearance, much as they would use cosmetic surgery or even a new hairstyle. The treatments can be used to straighten, lighten, reshape and repair teeth. Cosmetic treatments include veneers, crowns, bridges and tooth-coloured fillings.

"As people live longer, dentistry requires ever more restoration of shapes, colours or alteration of the teeth. Teeth rejuvenation is today done with new ceramics on the original tooth and sophisticated gluing techniques which result in younger looking teeth, more functional than original dentition. The outcome of cosmetic dentistry can be aesthetically and functionally spectacular (see photos below): teeth look younger: technologies with new materials have evolved which guarantee longevity and resistance of those new teeth so that they not only look even better than the original dentition but they last longer" (Dr Kulen[65]).

[65] Unpublished paper and photos "Vieillissement dentaire" (2007), personal communication.

Effect of Cosmetic Dentistry Treatment: Before / After



Source: photos © Dr Kulen, 2007

5.6.6. Brain Enhancement and Brain Training

Background: Cognitive enhancement is a new research field but also is attracting a range of consumers. Internet websites promote today the "Smart Life Style" where tools are given to consumers on how to manage their brain performance, counter-act the signs of age and boost their neurons at the same time. This quest for a sharper mind has triggered a new business venture to target the population interested in mind matters such as thinking, reasoning, emotions, spirituality, creativity, sleep, sex, curiosity, memory, and the myriad of mental possibilities of the human being.
Interventions range from neurological engineering to pharmacological intake via dietary styles, brain training tools and computer games.

As reviewed above, many substances, such as dietary and speciality supplements, hold positive or negative effects on the brain's neuroactivity and hence on the brain's performance. On the other hand, much research is underway in top academic institutions, such as MIT, to manage and restore memory, either by administering medicine that mimics the memory-boosting effects of enriched environmental conditions by a DNA vaccine, or by neurologically engineered implants. Despite the promising venues, the current tests are conducted in animal models and are too few to be considered as potentially applicable to anti-ageing medicine. We will consider some of the latest developments in consumers' brain training and programmes.

Scientific evidence: As seen in the preceding chapter on better ageing, consistent findings increase continually demonstrating that mental as well as physical training have beneficial effects on improving cognitive, reasoning, and memory performance in healthy ageing persons up to over 80 years old. What is less known is the scope of these effects when it is only used on a certain group (e.g. young adults, patients with specific diseases) are suddenly put on the market with the claim of improving consumers brain performance; this is the case with computer games for older generations, brain training, or self-monitored bio/neurofeedback systems for the daily control of brain waves.
Two examples are presented below.

a. "Brain Age" Nintendo Game

Usually focusing on children and teenagers, new technologies and computer-based games are in full expansion and propose tools for "Brain Training" targeting adults and older adults. "Brain Age" was developed in Japan. This computer programme launched by Nintendo in May 2005 as the new generation of brain training games was called "Train your Brain in Minutes a Day!"

The motto, "If your brain is older than you, you should take note! Your brain is older than you are but you should train it daily." (Scientific American, 31.5.2006) Brain has an age of its own, independent of the body; by using it, it rejuvenates. The purpose of the game is to get your own brain age as slowly as possible. The ultimate goal and ideal score is to obtain a brain age of 20! The controller calculates a score on various games and places the score on a curve obtained from testing real people aged 20 to 70 years old. It only requires that we scribble with a plastic stylus. Brain Age ($19.99; Nintendo DS controller, $129.99) can be ordered from all over the world through internet (www.brainage.com). In 2006, Nintendo had sold more than 5 million copies of "Brain Games" in Japan alone.

Other companies are developing technologies for brain training such as "Learning Enhancement Corporation's BrainWare Safari", and "CyberLearning Technology's Smart BrainGames". The particularity of "'Smart BrainGames" is that the user is playing a racing game on a Sony PlayStation while wearing electrodes to monitor brain waves. The game was first intended for children with attention difficulties or patients recovering from brain injuries.

b. Mental Aerobics or Mental Exercise through Brain Wave Feedback

Anti-ageing medicine is using mental exercise to practice brain control in everyday life. Many mental illnesses are accompanied by unusual brain-wave patterns. The experimental therapy, also called EEG biofeedback, aims at improving cognitive performance. Receiving such information from monitoring devices makes normally undetectable body functions accessible for conscious regulation. A person can realise from listening to his racing pulse, for example, that he is under strain and can thus learn to bring his heart rate under control as demonstrated in research on animals and epileptic patients by a number of teams (Prof. Barry Sterman and his team at the University of California Los Angeles: Sterman and Friar, 1972; Sterman, 2000; and Niels Birbaumer and his colleagues at the University of Tübingen: Birbaumer, 2001, 2006; Birmbaumer and Cohen, 2007). Regardless of frequency, there is no magic formula for learning to harness one's brain waves. Each subject must discover his or her own individual strategy by trial and error.

In addition to therapies, neurofeedback as a 'Brain Booster' can also improve cognition in healthy brains. A study published in 2003, carried out at the London Imperial College, supports the idea that brain-wave training can improve cognition, musical ability or train people whose professions require exceptionally steady hands such as eye surgeons (see Scientific American Mind, February 2006[66]). Six steps to maximise brainpower are proposed by some AAM protagonists (Miller and Reinagel with the Life Extension Foundation, 2005): basic nutritional support, physical exercise, hormone balancing, mental exercise, stress reduction, and targeted brain nutrition.

Boosting the brain, besides a healthy lifestyle, is advocated by AAM through many new ways in order to reach 'Peak Brain Function'. Given that depression and suicide are the most serious mental health conditions in old age,

[66] Scientific American (February 2006), "Train Your Brain" by Ulrich Kraft. See:http://www.sciam.com/article.cfm?articleID=000C075D-4357-13D9-810183414B7F0000

suggesting to people that they should maintain a good brain function will need to be assessed along with quality of life and satisfaction measurements. If it can be proved that such tools can enhance health subjectively and alleviate mental health problems, often linked to the feeling of worthlessness in retired elderly, it will be an important factor for improving health and longevity of the ageing population.

Conclusion: The examples presented show that not only people can take charge of their level of training but that a new field of self-monitoring therapeutic tools available to all is entering the market. Apart from a positive recommendation to further encourage a people-centred approach to brain training and social interactions such as in "Brain Age", no risks are known today in the use of such tools.

The ethical dilemma posed by such games is that ageism is associated with a measurement that suggests a peek brain performance of "age 20" and not as a simple "measurement score". One can wonder, "why not 13 years old?" Two years of launching these tools no specific research has been conducted on those games, but it will be necessary and also interesting to deal with the confusion, for example, between brain performance and knowledge management. On the other hand, by controlling their brain waves, the patients' practice with neurofeedback may also benefit those who suffer from epilepsy, attention deficits, stress, depression, and other debilitating mental disorders.

5.7. AAM Interventions: Benefit or Illusion?

5.7.1. Need for Evidence

Even one of the strongest opponents of anti-ageing medicine and former director of the "National Institute on Aging", Dr Butler, recognises that "not everything we hear about anti-ageing is hype. Although the question remains open, the present state of our knowledge is somewhat encouraging, based on results with laboratory animals" (ILC, 2001).

The first scientific evidence came from the longevity-extending caloric restriction experiments in rodents by McCay et al. (1935). However, experts met to

discuss the validity of such research in humans and came to a general consensus that neither similar genetic modifications nor voluntary caloric restriction *per se* deserved serious consideration as an intervention in humans. The importance of these research findings in animals is as follows: 1) ageing can be slowed dramatically in model systems through simple means, and 2) they point to promising directions for research that could lead to practical pharmacological approaches that effectively decelerate ageing, thus preventing or delaying the occurrence of a wide range of age-related pathologies in humans.

Modern technology has clearly made great progress toward improving human health, health behaviour, and access to health, thus enabling greater numbers of people to reach old age. This is one of the great achievements of public health as well as of modern technology and medical science.

Furthermore, evidence today underlines the body's intrinsic capacity for self-maintenance and repair which brings a more realistic and promising approach in ageing intervention and prevention. This is based on observations that exposure to low levels of otherwise harmful conditions can stimulate homeodynamic adaptive responses that benefit individual cells as well as the whole organism. The fact that low doses of toxic or harmful substances have a protective effect is known as hormesis.

Hormesis: Activity and Minimal Stress to Slow Down Ageing

Although the hormesis concept has been defined in different contexts such as pharmacology and toxicology, hormesis in ageing is characterised by the beneficial effects that result from cellular responses to mild repeated stress.

According to Rattan, exposing cells and organisms to brief periods of stress should therefore slow down ageing, since the hormetic response to the stressor not only defends the organism against the stress but also overreacts to remove other accumulated damage in cells and tissues. The paradigm for hormesis is exercise, an activity that is both stressful and damaging due to the production of free radicals, acids, stress hormones and cell and tissue breakage. But as an inducer of repair and maintenance processes, the hormetic effect of this strenuous activity has a wide range of health-promoting effects.

> Applying hormesis to slow down ageing from within, prevent the onset of age-related diseases, and maintain physical and mental abilities in old age is a real possibility. But much more research on the molecular and physiological effects of mild stresses on the human body is needed before we can develop effective means of ageing intervention and prevention.
>
> (Rattan, 2005)

Many anti-ageing interventions, whether proven on animals or partially on clinical cases, remain as 'working hypotheses' as progress in technological tools, research, and findings proceed. The interventions presented above give the impression that such interventions are not always useful and may even be dangerous; it may well be that in a year from now some research discovery will have brought new evidence by either indicating a risk factor, or by proving their benefits. The objective of the research is then to clarify, as far as possible, the grey areas to determine what offers convincing results (for different age groups, gender, metabolic and health condition) and what offers only occasional results and remains to be proven. The fundamental dilemma for users and consumers is getting correct scientific information and not misleading information constructed solely for marketing purpose and which puts the user at high short- or long-term risk.

As demonstrated by the evolution of evidence in HRT for menopaused women, some inherent methodological bias of research or confounding and interactive correlations between all those factors are possible, and it is now simply a matter of further research in the complex field of multiple preventive interventions on a given human, group or population.

5.7.2. Need for Standard Indicators and Procedures

Most biogerontologists and public health specialists would agree that not only do we have reliable biomarkers today for high-risk conditions, but that we also need new ones with a more integrated approach. As seen in the first part of this report, some risks are modifiable in healthy people but also in acute conditions and even in some chronic situations. Therefore, it is important to distinguish between modifiable and non-modifiable biomarkers for a specific population vs. general population.

A number of these tools already exist today in preventive medicine. As new technologies progressively become cheaper, more accessible and user-friendly, new testing measures will be available (e.g. the use of MRI or PET for prevention of diverse cancers such as prostate cancer). The pharmacological sector is very interested in research, refining, translating, and validating more clinical biomarkers as they hold the promise of ensuring efficiency of treatments and preventive interventions.

From an anti-ageing medicine point of view, biomarkers would be of great validity and could be worth developing in testing not only hormonal, but also dietary and pharmacological interventions to delay or reverse certain metabolic manifestations of ageing. The anti-ageing industry has promoted a variety of compounds to compensate for the changes of many metabolic markers with age. The question is: “Can they be considered biomarkers of ageing?” For example, it could seem reasonable to think that hormone therapy strategy is more likely to be beneficial as high levels are found in youth compared with the lower levels found in older people. However, this ignores the possibility that the declining hormone levels may represent a protective mechanism against the development of late-life pathologies such as cancer, diabetes or cardiovascular diseases, about which we still know little, so that and only long-term research can give us an answer. Along the same lines, extending healthy quality of life from the anti-ageing point of view takes a multi-factorial approach to disease prevention right down to the human cells, the smallest units of living matter capable of functioning independently. Biomarkers should also integrate a ‘control system’ working on the four key molecular or biochemical processes central to AAM and central to ageing as well as many diseases of ageing: oxidation, inflammation, methylation, and glycation (Miller and Reinagel, 2005).
The choice of interventions and how they are administered requires more knowledge than is currently available before offering proof of safety of any molecule or product. The hope of biomarkers is their important and potential role in validating interventions and treatments, and helping accelerate market withdrawal procedures when needed.

Summary: The anti-ageing medicine movement, started in the 90s in the United States, has grown today into worldwide multi-stakeholder networks (including patients) organised to exchange scientific data, establish a continuous education and promote AAM, which covers interventions, products and even clinics. While anti-ageing is not recognised as a specialty by the academic institutions, the movement is constantly growing beside the expansion of a fruitful business.

Scientific perspective: Anti-ageing medicine is of interest and concern to many medical and biomedical disciplines. While there is a consensus that many findings are promising in animal and human clinical research for the numerous interventions and products labelled as anti-ageing, there is still too little or inconclusive evidence for most of them. While some interventions do simply not work in healthy persons, but may or may not work in people with the specific deficit given their age, sex, or general condition, other interventions work in healthy persons but are not recommended in specific populations (e.g. age, gender, unhealthy). Given the lack of consensus and the diversity of methodological issues, there is a need of investment in differential basic and clinical trial research in biomarkers and interventions, before generalising data too hastily to the general population. AAM remains a new important public health concern and needs thorough standards of research before conclusions and public decisions can be rendered.

Clinical perspective: Many interventions are efficient, some at high risk for specific conditions; given the rapid anti-ageing development, new systems of monitoring scientific findings, prescription regulation and continuous education for clinical practice are needed. On the other hand, non medical anti-ageing practices need thorough supervision and regulation.

Consumer perspective: The central issue is the right and need of citizens to buy safe products and interventions. The problems are two-fold:

(i) the government 'approves' drugs differently from dietary or speciality supplements—so as many anti-ageing products are not regulated as medications, they do not go through the rigorous safety and efficacy testing that most prescription drugs face, thus safety of the product is at stake;

(ii) the private sector can market some anti-ageing products with information misusing scientific findings with fallacious effects (or hidden risks), thus misleading the consumer; those industries operate for their own financial benefits and no frontiers—often sold at the international level with direct mailing or internet (e.g. the case of Braswell see GAO, 2001).

6. Anti-Ageing Medicine in Switzerland

By Babara So-Barazetti, Evaluation Consultant

Summary: This chapter presents findings regarding the practice of AAM in Switzerland. They are based on desktop research and interviews. In Switzerland, anti-ageing medicine is mainly understood as aesthetic improvement, improvement of quality of life and as early prevention of age-related problems. Although a number of treatments and products are available through non-medically qualified practitioners or on internet, the chapter focuses on AAM practiced by the medical profession. Practitioners come from a number of disciplines and practice AAM mostly in addition to their conventional activity. Formal training for AAM is not (yet) available, but the theme is gradually introduced in further education programmes for the medical profession. Medical societies or working groups for AAM have emerged and are active. Besides other motivations, practitioners are drawn to AAM for its exciting potential in both academic and financial terms. AAM consumers are mostly self-payers. They are seeking a more youthful appearance, an assessment of their health and their health risks, advice on lifestyle and on various available treatments. In the absence of neutral and easily available information on AAM, they rely on their doctor's recommendations and rarely inquire into the usefulness, efficiency, (cost) effectiveness or risks of the proposed diagnostic tests or treatments and interventions. In Switzerland as elsewhere, AAM is an emerging branch of medicine and a growing market. It is characterised by different mechanisms from the curative market in terms of consumer attitudes, financing and regulation. The offer covers a wide range from conventional preventive advice to highly controversial treatments. Legal and regulatory issues that need to be examined in relation to AAM are: sales over the internet, offers by non-medically qualified persons, medical training and practice, advertising. Practitioners as well as patient and consumer organisations feel that these issues will become increasingly problematic and will need to be addressed. Other identified problems and challenges concern information, leadership and policy. As action is needed on many different levels, it is suggested that an appropriate agency or institution be given a coordinating role for concerted action to be initiated and pursued.

In Switzerland, as elsewhere, anti-ageing medicine is still ill-defined and health professionals, as well as the public, may understand it in many different ways. For some, AAM is near preventive medicine and health promotion ("but taking a more active approach"), while for others it also includes appearance or wellness medicine, and still others are more interested in anti-ageing or longevity research. For this reason, the investigation in Switzerland was broad, i.e. it included all of the above and thus provided the heterogeneous picture of AAM that is presented in this chapter.

The findings presented below are based on web-based research, grey literature as well as on visits in clinics and interviews with actors in the field of AAM in Switzerland, mostly medical practitioners.[1] The focus was on patient/client directed activities. Some additional information was obtained on medical societies, the anti-ageing market, the viewpoint of patients and consumers and some legal and regulatory aspects. Information on anti-ageing research in Switzerland was obtained from two leading figures in the field, with additional information coming from practitioners. However, no attempt is made to provide an exhaustive overview of AAM research conducted in Switzerland.

As anti-ageing medicine is often intended for people who are in good health rather than for medical patients, and is mostly financed by the patient/customer—the following text will refer to 'customers/clients' or 'patients'.

6.1. Methods

The initial desktop investigation covered clinics whose advertisements or website made reference to 'anti-ageing'. At that stage, establishments offering predominantly cosmetic/aesthetic surgery, wellness or beauty programmes were excluded. Interviews were then conducted with a range of practitioners from such clinics and with some other professionals known to be involved in anti-ageing medicine (including appearance medicine) and/or research. 'Appearance medicine' was included as it became increasingly clear that for

[1] In the French-speaking region, most interviews were conducted by Astrid Stuckelberger and Philippe Wanner.

many AAM means just that. Representatives of patient and consumer organisations as well as representatives of two medical societies/working groups and from industry were also interviewed. 21 interviews were conducted lasting from 45–120 minutes either on the clinic's premises or over the telephone. These were transcribed and their content analysed.

This cross-sectional approach made information gathering from and about a wide variety of health professionals in the anti-ageing field with backgrounds such as: general medicine, gynaecology, endocrinology, phlebology, dermatology, biogerontology, clinic director, patient organisation, consumer organisation, CEO of start-up company. It was felt that the selection of interviewees was fairly representative as it included not only many disciplines but covered also a very wide spectrum of settings (important private groups of clinics, small private clinics, private practice, start-up company, universities and research, 4 Swiss-based AAM societies, other medical professional associations/societies), activities and approaches (evidence-based approach, 'alternative' or 'experimental' approach) and the main pillars of anti-ageing medicine: lifestyle advice and conventional prevention, nutrition and vitamin supplements (orthomolecular medicine), hormone treatment, appearance medicine. However, in the selection process there may have been an overrepresentation of practitioners with a particularly well-advertised activity. While most of the information was gathered by direct interview, some additional information was obtained through web-based research and grey literature. This brought up additional facets—either of the market: high cost, explicitly profit-oriented, with/without control mechanisms—or of practitioners: with 'colourful' backgrounds, engaging in controversial (possibly illegal or unethical) practices, business-oriented with entrepreneurial activities.

Table 10: Areas Represented in the Interviews and Web-Based Research

Professional backgrounds
- general medicine
- gynaecology
- endocrinology
- phlebology
- dermatology
- biogerontology
- clinic director
- patient organisation
- consumer organisation
- CEO of start-up company

Settings
- Important private groups of clinics
- Small private clinics
- Private practice
- Start-up company
- Universities and research
- 4 Swiss-based AAM societies
- Other medical professional associations/societies

6.2. Results

6.2.1. The Meaning and Positioning of AAM in Switzerland

In Switzerland, the objective of anti-ageing medicine is mainly understood as aesthetic improvement, improvement of quality of life and early prevention of age-related problems. This includes a wide spectrum of approaches, some evidence-based, others speculative. Conventional lifestyle advice (prevention), as well as maintenance of patients' peak performance for as long as possible and claims for 'youth restoration' may all go under the name of 'anti-ageing medicine'.

The interviewed professionals mostly dislike the expression 'anti-ageing'. Nevertheless, it was felt that despite its shortcomings, the expression should be maintained as it is now commonly used and 'understood' by the public. Some

feel that 'better ageing' would have been a more appropriate expression, others underline that the link to 'prevention' needs to be made clear.[2]

On account of the high profile and the attention that the media pay to appearance medicine, the public seems to equate AAM to plastic surgery and dermatological interventions. Yet the medical profession emphasises the transversal nature of AAM and most agree that it must remain interdisciplinary. AAM is often associated with primary prevention and health promotion (promotion of a healthy lifestyle), but it seemed necessary to take a more active approach. Despite claims to interdisciplinarity, some medical disciplines—through their professional associations—seem to 'fight' for occupying the 'anti-ageing territory'.

Practitioners and patients/clients are all confronted with the difficulty in obtaining, assessing or understanding information on AAM approaches and treatments, as data and information is widely dispersed and coming from many sources. Moreover, the reliability of the sources of such information is not ensured.

In fact, AAM in Switzerland mostly consists of extensive diagnostic procedures (taking the patient's history, laboratory, and other tests), followed by advice or therapy/intervention. Depending on the practitioner's approach and speciality, these are usually: aesthetic improvement, lifestyle advice (more 'conventional' health promotion or prevention), hormone replacements/supplements and nutritional supplements (orthomolecular medicine). Other therapies such as detoxification (chelation), mesotherapy (microinjections) or animal cell therapy are marginal yet available in some clinics. Most of these interventions are on a self-paying basis, but some practitioners allow or encourage a mixture of insurance-based and self-paying.

6.2.2. The Practitioners of Anti-Ageing Medicine

Profile: AAM is practiced by doctors from a variety of disciplines, and a broad range of approaches is on offer: some conventional, others alternative or controversial. Anti-ageing medicine, interpreted in such a broad way, is available both in hospital settings and in private clinics and surgeries, but is

[2] This is exemplified in the name that one Swiss AAM society has adopted: Swiss Society for Anti-Ageing Medicine and Prevention (SSAAMP). More recently, one of the very reputable AAM journals has changed its name from 'Anti-Ageing-Medizin' to 'Arzt und Prävention'.

most often practiced within the private sector. The profile of doctors offering AAM goes from highly respected professionals (e.g. leaders in their field) to those working in a more unorthodox way (e.g. banned from practice in another country, advertising controversial therapies or making unethical claims).

Besides being practiced by specialists from the more obvious disciplines such as endocrinology, dermatology, and gynaecology, AAM is sometimes also offered by sports' medicine or in general practice. Geriatricians, rheumatologists, and neurologists do not usually use the expression of AAM although some of their activities would certainly appear to include "measures that slow down, stop or reverse the ageing process".

Anti-ageing medicine, excluding appearance medicine, is rarely the main activity of an individual practitioner or a clinic but is usually practiced in addition to the core activity.

Training: Specific and comprehensive training in AAM is not yet available in Switzerland. So far, interested practitioners have acquired their knowledge through individual participation in training opportunities and at meetings abroad and more recently also in Switzerland (see also 'AAM societies').

It appears that most university hospitals are increasingly interested in the issue. While 'ageing' and its mechanisms have been a subject of basic medical teaching for some time, 'anti-ageing' is starting to be taught in seminars and further training for professionals ('Fortbildung') and gives credits. This could be regarded as some 'official' acknowledgement of AAM.

In at least one institution, efforts are made to bring together specialists from various fields sharing a common interest in AAM. These initiatives are not institutionalised but are initiated by interested doctors.

As AAM being interdisciplinary by nature, its positioning within the present academic structures will remain a challenge for some time to come. There seems to be a clear call for an institution to take the lead in this matter, but the obvious disciplines (preventive medicine) seem reluctant.

Motivation: Practitioners are motivated to include anti-ageing medicine into their other activity for many reasons. The following were mentioned:

1) perceived need of patients to receive a more 'holistic' approach than one that can be offered by the conventional specialist's approach;
2) the practitioner's own need for collaboration with colleagues;
3) academic curiosity;
4) practitioners' economic need to attract more patients (see also section about the anti-ageing market);
5) exciting potential for the future, both academically and in terms of private practice.

Academic interest: Practitioners do not participate much in clinical research or research projects while acknowledging the need for research yet regretting a lack of time or the existence of coordinating groups (in order to conduct multi-centre studies). Another problem is lack of funding: it has been observed that funds are scarce for research into non drug-based approaches (e.g. stress management or other preventive measures) or non-patented substances such as DHEA and melatonin.

It was mentioned that AAM was rarely practiced according to well-defined protocols so that comparable clinical data is therefore difficult to obtain. Where protocols exist (e.g. for Botox applications and filler injections), adherence is voluntary. An exception to this was mentioned: the Lipolysis Network.[3] All Lipolysis practitioners work according to a highly structured protocol, so that every patient is treated in the same way, with the same products, and even with the same needles in order that eventually results can be pooled and analysed.

Fundamental as well as applied clinical research into AAM is conducted[4] at Swiss universities and in research laboratories run by industry. The academic world and university hospitals are also showing increased interest. Academics and clinicians from various disciplines are getting involved in various ways:

- they take part in the academic and sometimes public debate (publications, media presence, etc.);
- they either conduct or direct research activities;

[3] http://www.network-lipolysis.com

[4] This investigation did not focus on research activities in AAM in Switzerland, but has established that researchers from Switzerland are involved with anti-ageing research and are regularly making contributions at international meetings and conferences.

- they sometimes provide information for the general public;
- they offer some anti-ageing advice/therapies as part of their clinical activity;
- they introduce the subject into their respective disciplines or societies ('Fachgesellschaften') or into their teaching;
- they seek transdisciplinary collaborations and/or defend their territory;
- they have a commercial interest in AAM products or services (production of creams, food supplements, diagnostic tests, etc.).

Commercial interest: The commercial aspect of AAM is undeniable and was mentioned by most interviewees. In terms of financing and regulations, anti-ageing medicine as a whole is characterised by different mechanisms from the curative market and follows the logic of a consumer goods market. AAM is therefore more aggressively advertised than other medical activities. Private practitioners sometimes use professional help in patient acquisition; waiting rooms are well-stocked with brochures about available diagnostic tests, treatments and products. University appointed academics or professors may either work in (their own) private clinics/practices, or they may be involved in the marketing of products and services.[5] At least two of the AAM societies in Switzerland (see following section) are quite strongly linked to industry; one appears to be entirely industry-driven, the other is conspicuous for the complex and wide-ranging web of professional and commercial links between the (committee) members and industry. It appears that industry and business are wooing AAM providers with particular insistence.

QUOTES:

"Nowadays, many colleagues just manage to cover the costs of their practices […] The Eusana concept consists of an expert system for health and preventive medicine and of an individualised concept for patient acquisition."[6]

[5] Examples include: professor of gynaecology with start-up company producing anti-ageing cosmetic cream using cultured foetal skin cells; professor of surgery producing his own prescription hormone-enriched hydration cream; professor of gynaecology involved with company offering genetic testing; associate professor of dermatology running his own liposuction clinic.

[6] Extracted from an advertisement: in German: "Heute decken viele Kollegen gerade noch die Kosten ihrer Praxis […]. Das Eusana-Konzept besteht aus einem medizinischen Expertensystem für Gesundheit und Präventionsmedizin und einem individuellen Patientenmarketingkonzept."

> "It is not easy to resist industry. They come and knock at your door all the time, they present their new fabulous and fantastic products which are very expensive but very good."[7] (clinic director)

6.2.3. The Societies for Anti-Ageing Medicine

In the last few years, some groups/societies representing various approaches of anti-ageing medicine have emerged. They were mostly set up by one or several interested individuals and have developed quite independently from each other.

- *SAABA* (Swiss-Austrian Association for Better Ageing) was founded by gynaecologists in 2002 as an informal working group. It was founded specifically to create AAM training opportunities. It was also felt that the public needed warning about the misuse of products and the group (today called SABA, see below) still considers it as one of its main objectives.[8] The focus of the group was more specifically on hormone replacement, but from the beginning had included other aspects of AAM. One of its founding members is considered by many to be a leading figure in AAM: he favours general polymorphism screening[9] and individualised hormone replacement therapy. The approach is controversial not only on scientific grounds but also in terms of ethical and socio-economic concerns. The group no longer exists.
  Activities: The group initiated an annual training week ('Fortbildung') in gynaecology with a module regularly dedicated to aspects of AAM.

- *SAABA* later became SABA (Swiss Association for Better Ageing) and is reportedly integrated into the important Swiss Society for Gynaecology and Obstetrics (SGGG)[10] as a special working group. However, no reference to the group is found on the society's webpage. The society has dedicated one part of its last General Assembly to 'Better Ageing'.

[7] Original in French: "Il faut pouvoir résister aux industries qui viennent constamment taper à votre porte, vous présenter de nouveaux produits qui sont fabuleux et fantastiques, très chers, mais très bon."

[8] "We started because we wanted to stop the misuse of products, as it became more and more apparent that we are going the 'USA way'. It's still one of our main missions. That's why we underline the negative aspects and keep on warning." (personal communication)

[9] The screening is available by a company with close links to its founder member. Brochures are distributed in AAM practitioners' waiting rooms.

[10] http://www.sggg.ch/

Activities: Organisation of training modules in AAM (see above), plans to elaborate guidelines and standards regarding diagnostic tests, prevention and treatment of age-related problems.

- SSAAMP (Swiss Society for Anti-Ageing Medicine and Prevention) was founded in 2005. The focus of this society is on prevention,[11] in particular anti-ageing and modern orthomolecular medicine, but members of the board also include a surgeon, an urologist, a gynaecologist, and others. The society's main aim is to create training sessions for its members, to promote research, defend its members' interests and take a stand on matters concerning AAM and other related themes.
  Activities: The society organises an annual congress as well as regular and well-attended training sessions for its members and issues also a 'seal of approval' for selected products. The society and in particular its president[12] receive regular media coverage SAAAM (Swiss Academy of Anti-Ageing Medicine). Little information is available about this group and the persons or organisations behind it. The academy is a "non-profit medical association that organised a medical congress on new trends in longevity medicine & aesthetic medicine in December 2007 in Geneva" with 3,000 attendees announced. The society has no other activities. Its aim is "to promote a scientific exchange in the fields of Aesthetic Procedures, Integrative & Longevity Medicine and the Anti-Ageing effects of Laser & Light". Besides international speakers, a good number of Swiss doctors from various fields will chair sessions on topics such as melatonin, orthomolecular approaches, nutrition and osteoporosis, HGH, surgical techniques, etc.

The two groups that are taking an active part in the public and scientific debate are SABA and SSAAMP. Both are based in the German part of the country and

[11] "Wir können und wollen das Älterwerden nicht verhindern, sondern möglichst langsam gestalten. […] Über die drei Bereiche Prävention, kosmetische Chirurgie und Komplementärmedizin soll dies erreicht werden. Prävention steht dabei an oberster Stelle. Ein ethisch vertretbares Anti-Ageing ist ohne Prävention undenkbar." (http://www.ssaamp.ch) (We don't want to stop the ageing process but slow it down as much as possible. […] We try to do this with prevention, cosmetic surgery and complementary medicine. Prevention is the most important. Ethical anti-ageing medicine is unthinkable without prevention.)

[12] The president also runs his own private practice, is the medical director of a clinic and of another centre, as well as the managing director of a company producing orthomolecular products.

within these groups the French and Italian speaking members appear to be in a minority.

Both groups are actively pursuing AAM issues through training of their members, evaluation of new methods and approaches and information for the public. Both groups wish to develop guidelines. The groups are not on opposing sides of the AAM spectrum (some practitioners belong to both groups) but are clearly seen as representing different approaches of AAM. The media seem to be aware of it and carefully represent the views of both groups.

A certain amount of 'jostling for position' can be observed between the two groups but also between the various medical specialities concerned by AAM. Gynaecologists, for example, take the view that they are best positioned to advise women on questions of prevention and lifestyle (not only hormones) from an early age while others make claims to a more holistic and interdisciplinary approach. The observation that gynaecologists in particular are increasingly claiming AAM for their domain is not only true in Switzerland, but is observed internationally.[13]

6.2.4. The Consumers/Patients of Anti-Ageing Medicine

According to the interviewed practitioners, their clients/patients are mostly between 50 and 80 years old and are seeking to optimise their appearance or performance to delay or alleviate symptoms of ageing and to prevent the onset of disease. The majority of clients are women, but younger women and men are now consulting more frequently. As most AAM is self-paying, patients tend to be from a high socio-economic and educational background. Some clinics also attract foreign clients. However, after the introduction of some cut-price offers in appearance medicine, consumers from a more modest socio-economic background are now seen in clinics. Apart from seeking a more youthful appearance, patients are generally interested in an assessment of their health and their health risks. They are seeking advice on their lifestyle with regards to health and on various available treatments in the AAM market. Some are critical to a proposed course of action but most are happy to follow advice and rarely inquire into the usefulness, efficiency, (cost) effectiveness or risks of the proposed diagnostic tests or treatment/intervention.

[13] In 2006, the first European Congress for AAM was held, in conjunction with the Menopause and Andropause Congress.

Patient and consumer associations were interviewed. They both reported increasing enquiries regarding appearance medicine but were not aware of particular enquiries from patients/consumers regarding other aspects of AAM. Both organisations point out that the lack of enquiries or complaints cannot necessarily be interpreted as absence of need. They underline that patients and consumers regard health matters as a very private activity and that they would not necessarily come forward in case of problems. Both associations are aware of some problems related to AAM but do not have access to some case histories.

QUOTE:

"It is the same as for dieting and weight loss products: people are reluctant to come to us when they encounter problems. For AAM it is the same. But this does not mean that problems do not exist."[14] (Swiss Patients' Organisation)

The increasing offer and demand in AAM is accompanied by the consumers' difficulties in obtaining fair and impartial advice and information. The issue of quality assurance is also becoming increasingly urgent. In appearance medicine, a private company[15] has started to certify clinics and practitioners that satisfy its reportedly stringent quality controls. Advice about treatments and addresses of certified surgeons and clinics are available for a fee. The Swiss Consumer Association backs this private initiative, given that no other control mechanisms are in place and that information on quality is a need expressed by consumers and patients.

6.2.5. The AAM Market

The following observations are based on a recently published report on future perspectives for the health market in the whole of Switzerland (Sigrist, 2006) and some of the information may be indicative for the trend in the AAM market. Further information was obtained from interviews and existing literature.

[14] "Es ist wie bei den Schlankheitsmitteln: die Leute haben Hemmungen, mit Problemen zu uns zu kommen. Bei AAM ist es das Gleiche. Das heisst aber nicht, dass es keine Probleme gibt." (Schweizerische Patientenorganisation)

[15] ACREDIS: http://www.acredis.com

The size of the anti-ageing medicine market in Switzerland is difficult to assess. Firstly, it is a market that is conducted between provider and consumer and data on the volume of interventions or financial turnover is largely unavailable. Secondly, it is a highly diversified market and assessing the whole market would only be possible with an extensive aggregation of single markets.

In general, the curative health market is increasingly supplemented by a preventive health market, i.e. by products and services that aim at prevention of disease and maintenance of health. Increasing demand is already reported for the wellness sector, for functional food and for appearance medicine. It is reasonable to deduct that such an increase will be observed for other AAM sectors (e.g. hormonal supplementation, orthomolecular medicine, etc.). Apart from appearance medicine, there is not yet enough demand for AAM to be practiced on its own. Practitioners offer AAM in conjunction with other more classic disciplines and benefit from the synergy between the curative and the preventive market. Analysts are predicting that there is a high development potential—especially in the non-operative sector.

The preventive market is characterised by different mechanisms from the curative market in terms of consumer attitudes, financing and regulation. The new preventive offers are supplied in a free market where buyers' decisions are based on the logic of a consumer goods market. The following observations apply to only some segments of the health market (functional food, lifestyle medications, plastic surgery) but illustrate what may be the trend for AAM in general.

Functional food: The market for these products is difficult to estimate, but nonetheless is largest in the USA (2004: $19 billion), followed by Europe and Japan, and is continually growing. The data for the Swiss market is difficult to analyse: for example both *Nestlé* and *Emmi* are innovators in this sector and have clearly focused their strategy on this growth market. Nestlé reported a reluctant Swiss market for these products but predicted that demand would grow successfully in view of the success registered elsewhere in the light of the socio-demographic developments. The Swiss Consumer Association is alarmed at the strategies adopted by advertising campaigns for some of these products and has alerted the authorities. There is a challenge for industry and government authorities to provide or demand evidence on the health benefits of these products, in order to inform and educate consumers, as they are at the interface between a food and a pharmaceutical product.

Lifestyle drugs: The market for appearance and performance improvement is developing so that drugs (so-called lifestyle drugs) are an important area. These drugs are not intended to cure but to improve well-being and appearance. Antidepressants are sometimes included in this group and are so far the most lucrative market. Swiss pharmaceutical industries are not market leaders in this segment but have developed products such as *Xenical* (a dieting pill). The market in Switzerland is growing and an indication is the sale of products such as *Viagra* for erectile dysfunction (growth from CHF 30 to 40 million between 2003 and 2006)—where sales in Switzerland are third highest worldwide—and *Propecia* against hair loss where sales are also increasing. As these products are self-paying products, their increasing sales are also an indicator for the readiness of the Swiss consumer to invest in better appearance and performance. And it is predicted that the trend will continue. Many of the lifestyle drugs are not available in Switzerland and are bought via internet or through Swiss-based law-defying suppliers (see also section on legal aspects).

Plastic surgery: No precise data exists on the extent plastic surgery is used. Based on German data, 80,000 interventions a year are estimated for Switzerland. At an average price of CHF 5,000 turnover could be estimated at CHF 400 million per year. In Switzerland the market is still growing but in the USA it is stagnating. One Swiss clinic reported that the yearly increase of its interventions was 15% to 20%, since 2002. The number of specialists in Switzerland has grown from 71 to 117 between 1991 and 2004. The market has targeted a new, younger and less wealthy clientele to whom it tends to offer cut-price interventions or packages deals. Advertising has become more visible and surgery clearly has become a consumer good in this area.

6.2.6. AAM Practice in Switzerland: What is Available?

The presentation of a comprehensive picture of the vast and diverse AAM offer in Switzerland goes beyond the scope of this report, it is only an attempt to synthesise the findings, and emphasis is given to quotes illustrating the various points.

AAM is usually offered in conjunction with, or in addition to, other medical services. It is often kept distinct from the practitioner's main activity and sometimes proposed under a different clinic's name. The approach covers a wide range of offers, from conventional preventive advice to highly controversial treatments.

Some practitioners will take a thorough history, perhaps (computer-)assisted by a questionnaire and then proceed with advice on lifestyle or lifestyle changes and may propose some hormone or nutrition supplement.

QUOTE:

"I only do AA activities that have proved to be useful and where the risks are known; I only do tests that make sense, i.e. that can be followed up by preventive or therapeutic measures; I only propose tests and eventual therapies that are affordable to the normal population. In terms of hormones, I take a very extensive history (I have developed an extensive computer-assisted test) and from the symptoms, I can tell mostly what the patient needs." (gynaecologist)

Others will perform initial consultations and diagnostic tests in greater detail and at considerable cost. A very complete check-up with several consultations and tests, sometimes including genetic testing, can cost up to CHF 7,500 or even more. The results are often presented in a user-friendly way and in an attractive format for the patient.

QUOTE:

"The Youth Restoration Programme consists of a full laboratory and physical analysis of the status quo. Then all necessary hormones are replaced in the correct dosage to reach the levels of 25 to 30 year old healthy people. The organs are revitalised by 29 different foetal cell preparations that are injected intramuscularly. In addition, we recommend a hair mineral analysis to determine the nutritional status of the cells and the load of heavy metal toxins." (from the website of a general practitioner with anti-ageing 'clinic')

The proposed follow-up treatments are prescribed often on account of a 'deficiency' discovered. These prescriptions can cost as little as CHF 50 for nutrition supplements but up to CHF 18,500 for a series of Extract Revitalisation Therapy (cell extracts from animals).
Doctors are well aware that some of the diagnostic tests or treatments are not uncontroversial and that many of the treatments are not based on solid

evidence or are still in a grey zone. However, based on their own experience or that of others, they propose therapies that they judge to be harmless, though not necessarily efficient. This point is well illustrated by the following quotes:

QUOTES:

"… these are people who are living careful lives and who have no risk factor, neither genetic, nor behavioural, nor environmental. In such a case we can address the problem of ageing. In fact, we are a bit unease with the interventions that we can suggest. We know the theory. There are substances on the market that appear to be promising. But we are always a bit uncomfortable with the clinical application, because the products have rarely gone beyond the phase of animal testing …"[16] (specialist in the prevention of ageing)

"Patients have a lot of reticence. But after a test, when I can show them where are their deficiencies or some manifestations of, say, 'bad memory or loss of concentration', and when I can give them figures about the potential risks, they gain trust and are ready. But initially, they are reluctant. The studies are really not conclusive, so I listen to some trusted and experienced colleagues, because it really is a grey area. That's why I am very careful with hormones. I don't give growth hormone, DHEA yes, although there is potential danger. But all these people in the USA who are taking it, if it was dangerous, there would be some evidence for that, but nothing has emerged. This is not scientific (what I am saying), of course, but sometimes one has to trust one's own common sense." (plastic surgeon about hormone therapy)

Thus, a vast range of anti-ageing advice and therapies are available. Many are not evidence-based and some are applied by practitioners who—by their own assessment—are ill-prepared for the task (see also the following section on

[16] "… sont des gens qui ont fait très attention au cours de leur vie et qui n'ont pas de facteurs de risque ni génétiques, ni comportementaux, ni environnementaux. Dans ce cas-là, on peut s'occuper du problème du vieillissement. Ce qui est un peu gênant dans les interventions que l'on peut leurs proposer, c'est que, bien que nous connaissions la théorie, sur le marché, il y a des substances qui semblent intéressantes. Là où on est toujours gêné, c'est pour l'application clinique, parce que tous ces produits ont rarement dépassé le stade de l'expérimentation animale …"

medical training and practice). A leading figure in ageing research is categorical:

QUOTE:

"It is the practitioner who must judge himself/herself what he/she can do without too many risks, and what cannot be done, because the risk is too important […]. The ethical problem is also crucial for medical practitioners: if one engages in the specialty of ageing prevention, it is better to know what one is talking about. From a medical point of view, it is not ethical to give advice to or influence the behaviour of people if you don't have an appropriate knowledge and expertise."[17] (specialist in the prevention of ageing)

6.2.7. Legal and Regulatory Aspects

This report is not intended to cover all legal and regulatory issues that could be relevant to AAM in Switzerland. It merely reports on aspects that were mentioned in interview, often as an answer to specific questions relating to the interviewee's activity or experience.

The most frequently mentioned legal issues were related to internet sales of AAM products. Regulatory issues giving rise to some concerns are (1) offers by non-medically qualified professionals, (2) medical training and practice, and (3) advertising. Practitioners as well as patient and consumer organisations feel that these issues will become increasingly problematic and will need to be addressed sooner or later.

a. Internet Sales of Products

The unregulated and unsupervised sale and consumption of products sold via internet continues to be of concern. The variable quality of such products is documented. In Switzerland, Swissmedic is responsible for the supervision of all activities related to therapeutic products. Together with a working group of the Council of Europe, it has drawn up guidelines on the relative dangers of

[17] C'est le praticien lui-même qui doit juger ce qu'il peut faire sans risque et ce qui ne doit pas être fait, parce que le risque est trop important […]. Le problème éthique réside aussi avec les médecins, car si on décide de faire de l'antivieillissement, il faut savoir de quoi on parle. D'un point de vue médical, ce n'est pas éthique de donner des conseils ou d'influencer le comportement des gens si tu n'as pas les connaissances appropriées."

products bought online.[18] Suspect products can be stopped at the border, otherwise Swiss authorities can only take action if a website's server or a distributor is based on Swiss territory. If products are imported and sold directly to patients, it is the cantonal authorities that are responsible for action against individual illegal practices. Such practices seem to be quite common and at least one of the investigated AAM clinics in our sample illegally offers products bought directly on the internet to its clients.[19] However, action is usually only taken if a complaint is lodged with the relevant cantonal authority.

b. Interventions by Non-Medically Qualified Persons

Doctors as well as consumer and patient organisations are still concerned about some treatments dispensed by non-medically qualified persons. This mostly relates to abrasive dermatological interventions and laser or IPL treatments dispensed in cosmetic institutes. In fact, over the years, the Swiss Society for Dermatology and Venerology as well as Swissmedic and the Federal Office of Public Health have published recommendations, position papers and guidelines on the very issues that are causing concern.[20] The 'Schweizer Fachverband für Kosmetik' (SFK)[21] has started a quality control process and issues a quality label.[22] Despite these efforts it is felt that cosmetic salons are still dispensing such treatments, but remain largely unregulated. They are reported to be under even greater pressure from industry than medical practitioners to invest in new technology. The Swiss Consumer Association feels that clients are in need of some degree of protection.

In the future, the non-medical practitioners on the AAM market will increase. In the recent years private schools[23] have started offering courses leading to the

[18] http://www.swissmedic.ch/files/pdf/Leitfaden_AM_und_Internet-E.pdf

[19] "Kassenpflichtige Medikamente werden Ihnen von der Kasse zurückvergütet, die reinen Anti-Ageing Medikamente jedoch nicht. Letztere sind für Sie meistens in der Schweiz noch nicht erhältlich und können wegen der Zollbestimmungen für Medikamenteneinfuhr nur problematisch eingeführt werden. Wir bieten Ihnen deshalb an, alle Medikamente direkt und prinzipiell zum Internetpreis bei uns in der Arkadia Klinik zu beziehen." (www.arkadia-klinik.ch)

[20] For example, Swissmedic (1997): "Anwendung von hochenergetischen Lasern in Medizin und Kosmetik" or SGDV (2005): "Anwendung der IPL- oder Blitzlampen-Technologie in Medizin und Kosmetik – vor nichtmedizinischenm Einsatz wird gewarnt." (Positionspapier der Schweizerischen Gesellschaft für Dermatologie und Venerologie)

[21] Swiss Beauticians Union (cosmetic studios): http://www.sfkinfo.ch

[22] http://www.sfkinfo.ch/Portals/3/Info-Qualitätssicherung.pdf

[23] See for example: http://www.benedict.ch/be,me,173 "Anti-Ageing-Trainer/-innen sind als Berater/-innen von Hotels und Gesundheitseinrichtungen oder Fitness-Studios tätig oder arbeiten mit Ärzten oder Apothekern zusammen oder eröffnen selber eine Anti-Ageing-Praxis."

title of 'Anti-Ageing Trainer'. The school's advertising suggests that among other things, it would enable candidates to run their own practice. Thus, to the already ill-defined AAM market will be added a new category of non-medical 'professionals' dispensing advice and treatment. The need for some form of supervision or licensing may become urgent.

c. Medical Training and Practice

It appears that no standard curriculum exists for training doctors who wish to learn about AAM and no standards are in place regarding its practice. At present, the Swiss Society for Gynaecology and Obstetrics (SGGG) seems to be taking the lead by offering some training and information to its members.

Doctors as well as patient and consumer organisations have expressed disquiet about one particular aspect of medical practice: the fact that AAM practitioners commonly apply treatments that have little to do with their conventional discipline, on account of the blurred boundaries between disciplines that are typical in AAM. Examples can be surgeons who prescribe hormone treatments, or general practitioners who carry out invasive surgery, gynaecologists who mix their own face creams or dermatologists who inject cells or apply infusions. While it is legal for doctors to perform any medical act "done in good conscience",[24] it is widely felt that the market is forcing some doctors to push the boundaries of professional and ethical standards. This applies particularly to some articles of the "Professional regulations[25] of the Swiss Medical Association" which at times appear to be violated: medical practice (Ärztliche Berufsausübung, art. 3), controversial therapies (umstrittene Heilverfahren art. 8), duty to inform (Aufklärungspflicht, art. 10), limits of medical capability (Grenzen des ärztlichen Leistungsvermögens, art. 15); information and advertising (Information und Werbung, art. 20).

d. Advertising

AAM follows the rules of a market economy where advertising and sales of products and services are common practice. While a certain restraint is used in advertising medical services through the printed media, there seems to be widespread disregard for the existing regulations when advertising such

[24] Standesordnung FMH, Art. 3
[25] orig. "Standesordnung"

services on the internet. Industry regularly flaunts regulations when marketing its products.

Functional food is one such range of products and is described as a "growing and not clearly controlled market with a potential risk ranging from a particular food to a particular drug" (title of an editorial by the cantonal pharmacy of Zurich, 2004).[26] Although regulated by Art. 6 Abs. 1 LGV, the Swiss Federal Office of Public Health (FOPH) acknowledges (in a letter to the Swiss Consumer Association, 3/2/2006) that "the regulations are often not observed". If the Office of Public Health or the Consumer Association become aware of such abuse, they alert the cantonal authorities concerned who have the power and duty to take action. However, this is rarely done.

The rules for the advertisement of medical services are clearly described in the professional regulations of the Swiss Medical Association (FMH).[27] They stipulate, in particular for internet advertising, that "Informationen in zurückhaltender und unaufdringlicher Weise bekanntgegeben (werden sollen)", that "jede unsachliche, auf unwahren Behauptungen beruhende oder das Ansehen des Arztberufes beeinträchtigende Werbung (zu vermeiden sei)."[28]

Abuse of these existing regulations was found during the investigation for this report. Here also, better self-regulation by the profession itself would be desirable.

6.3. Problems and Challenges

Interviewees were asked for their views on present and future problems in the field of AAM. Based on their answers, the following provides an overview of the most pressing issues and makes some suggestions for action.

[26] http://www.smw.ch/docs/pdf200x/2004/25/smw-10748.pdf

[27] http://www.doktor.ch/homepage-doktor/standesordnung/standesordnung-rechts.htm

[28] "Information ought to be communicated in a restrained and discreet fashion, and advertising based on untruthful pronouncements or prone to compromise the reputation of the medical profession must be avoided."

6.3.1. Information

In Switzerland, there is no agreement on the definition or understanding of 'Anti-Ageing Medicine'. The word itself has negative connotations for some and there is a tendency to bring it back to 'prevention'. It is widely felt that AAM needs to be defined more clearly, and that the public in particular would benefit from clear and unbiased information. Impartial advice on AAM interventions, products, prices or merits and limits is either non-existent or not easily available to consumers and patients. Available information is dispersed on various internet platforms or elsewhere but difficult to locate or evaluate. Thus, the most pressing need seems to be for clear and well-founded information, easily accessible and coming from a credible and acceptable source. Professionals as well as the public need information as both are confronted with uncertainties. Professionals need information concerning the evidence and knowledge base for AAM, the public needs comprehensible information on the same issues, but also on the quality and safety of products, therapies and services.

6.3.2. Market-Driven Medicine

Commercial interest and industry play an important role in anti-ageing medicine. This influence may be felt in the way that AAM is practiced, in medical societies, evaluation, research and teaching. There are indications suggesting that supply and demand are partly induced by industry, that the market is growing and that Swiss patients/consumers are willing to spend on health maintenance, longer lasting high energy levels and youthful appearance. Given this growth forecast, more data and research is needed so that emerging 'problems' linked to AAM can be addressed. The AAM market—different from the curative market—needs new approaches with regards to regulation, information and communication.

6.3.3. Regulations

Anti-ageing medicine in Switzerland covers a wide range of the most diverse activities and approaches. Most doctors practice AAM in addition to their main speciality and the boundaries between one activity and the other are sometimes blurred. They are free to practice AAM in any way they judge appropriate. It has been stated that problems might emerge in terms of medical practice, medical ethics and sources of financial retribution (health insurance vs. self-paying). With regard to legal and regulatory issues, a gap exists between stated declarations and the reality of the situation. The challenge of bridging such gaps is

one of the issues that AAM will have to face. There is a clear call for better self-regulation and vigilance through the medical professional societies or through the FMH (Swiss Medical Association) and its cantonal associations concerning all legal and professional aspects. Particular disquiet was voiced regarding some widely used treatments such as Botox injections, as they could become an important long term health issue if side effects appeared.

6.3.4. Policy and Leadership

It is widely felt that so far the competent and authoritative institutions in Switzerland have not paid enough attention to this emerging field. The reality of AAM and its rapid development need to be acknowledged so that decisions concerning various aspects of AAM can be taken. On the policy level, for example, it must be decided if AAM needs to be addressed as a 'new' and distinctive field. A decision needs to be made whether AAM can be left to the market forces and thus be demand- and supply-driven, or if it should be regulated.

If we truly are witnessing a paradigm change from curative medicine to preventive medicine, then AAM would be directly affected. Its position within medical practice and its possible distinction from conventional prevention needs to be clearly defined. Logically, this discussion must precede the one about the merits (and the cost or possible reimbursement) of certain diagnostic and therapeutic measures.

The initiative for a concerted interdisciplinary approach needs to come from an established agency (e.g. FMH, BAG, SAMW);[29] a clear mandate to a mixed group of policymakers and experts should be formulated. Existing recommendations and guidelines are a starting point. However, in order to become effective, their content needs to be reinforced and repeated. In the absence of such an effort, information, regulation and communication will be mostly guided by private initiative (e.g. industry).

At an entirely different level, there is the societal approach to ageing which deserves to be brought to the public arena for the discussion to go beyond the mere care of the elderly. It has been suggested that the quest for youthfulness

[29] FMH – Foederatio Medicorum Helveticorum (Swiss Medical Association), BAG – Bundesamt für Gesundheit (Federal Office of Public Health), SAMW – Schweizerische Akademie der Medizinischen Wissenschaften (Swiss Academy of Medical Sciences).

may need to be counterbalanced by another attitude which is the recognition of the right to slightly diminished capacities with growing age, and that society ought to adapt to its ever ageing population and not vice versa—i.e. that the ageing population must adapt to an ever more youth- and technology-oriented society. Ethical and health-economic considerations may also require public and political debate.

In order to put some of the above into practice, an agency or an institution must be given a specific mandate and sufficient funding in order to coordinate the efforts required efforts on many different levels and with a large number of stakeholders. The chance to act sooner rather than later should not be missed.

Strategies:

In Switzerland there is no agreement on the definition or understanding of 'Anti-Ageing Medicine'. The word itself has negative connotations for some and there is a tendency to relate it to 'prevention'. It is widely felt that AAM needs a clear definition and that the public, in particular, would benefit from clear and unbiased information about its merits and its limits. Impartial advice on AAM products, interventions and prices, their benefits and dangers is either non-existent or not easily available to consumers and patients. Available information is scattered on various internet platforms or elsewhere and difficult to locate or evaluate.

Commercial interests and industry play an important role in anti-ageing medicine. This may influence medical practice and ethics, medical societies, evaluation, research, and teaching. The size of the AAM market in Switzerland is currently unknown, yet there are indications suggesting that offer and demand are growing and that Swiss patients/consumers are willing to spend even more on health maintenance, longer lasting high energy levels and youthful appearance. In the light of this growth potential, more data and research is needed to come to terms with these emerging and most urgent 'problems' linked to AAM. The AAM market—different from the curative market—needs new approaches with regards to regulation, information and communication. It is an established agency

(e.g. FMH, BAG, SAMW)[30] that should take the initiative for a concerted interdisciplinary approach giving a clear mandate to a joint group of policymakers and experts. Existing recommendations and guidelines are a starting point, but in order to become effective, their content needs to be reinforced and repeated. In the absence of such an effort, information, regulation and communication will be guided by private initiative (e.g. industry) alone.

AAM in Switzerland covers a wide range of activities and approaches. Most doctors practice AAM in addition to their main speciality and the boundaries between one activity and the other are sometimes blurred. They are free to practice AAM in any way they judge appropriate. It has been stated that problems might emerge in terms of medical practice, ethics and source of financial retribution (health insurance vs. self-paying).

On legal and regulatory issues, a gap exists between stated declarations and the reality of the situation. The challenge of bridging such gaps is one of the challenges that AAM will have to face. There is a clear call for much better self-regulation and vigilance through the medical professional associations or through the FMH (Swiss Medical Association) and its cantonal associations.

[30] FMH – Foederatio Medicorum Helveticorum (Swiss Medical Association), BAG – Bundesamt für Gesundheit (Federal Office of Public Health), SAMW – Schweizerische Akademie der Medizinischen Wissenschaften (Swiss Academy of Medical Sciences).

7. Socio-Economic and Ethical Dimensions of AAM

7.1. The AAM Economic Dimensions

7.1.1. Is AAM an Emerging Market?

In the demographic context of population ageing, health is definitely a promising market, with a wide variety of opportunities for entrepreneurship. Some of these opportunities require a high level continuous education in technological know-how from medical and non-medical practitioners. This is the case, for example, of certain advanced medical technologies and devices, but also of new diagnostic procedures, interventions or products. They generally develop in technical institutes or universities through small firms and start-ups, some of them can even get quoted at the Nasdaq.

Other products, such as dietary supplements, wellness, laser interventions, are more accessible to the private sector as they require less advanced technology. The market is therefore characterised by a multiplicity of products and actors, not necessarily efficient or safe. The economic dimensions of AAM are difficult to describe for various reasons linked to the very nature of the products and the ways they are consumed and acquired. The development of technologies is financed by different actors such as government, private and public research foundations, various investors, and consumers.

Example: *Sirtris Pharmaceutical*

Sirtris Pharmaceutical, in Cambridge (MA), was founded in 2004. It focuses on the development of Sirtuin drugs for the treatment of age-linked diseases and diet deficiencies (http://www.sirtrispharma.com). Sirtuins are a recently discovered family of enzymes that promote normal cellular function. In particular, Sirtuins improve the function of mito-chondria, which generate energy in cells. When organisms face adversity,

Sirtuins are activated as part of a natural process that maintains healthy function.

Sirtris does not provide a timeframe for its first drug to be commercialised, but it is estimated that the product will not be on the market before 2013. The company, however, is planning to enlist on the Nasdaq Stock Market at an unusually early stage in its development. It has raised a total of $82 million since its inception from investors including *Bessemer Venture Partners*, *Cardinal Partners*, *Cargill Ventures*, *Genzyme Ventures*, Novartis Bioventures Fund, Polaris Venture Partners, QVT Fund LP, *Skyline Ventures*, *The Wellcome Trust*, *Three Arch Partners*, and *TVM Capital*. After starting with a staff of 10 only it grew to 35 people between 2004 and 2006; *Sirtris* has hired an additional 25 contract researchers in Shanghai to benefit from lower costs and scientific expertise available in the county of Taiwan.

In Switzerland, according to the Swiss Biotech Association, approximately 250 firms are active in biotechnologies and 500 in medical technology.

Experts interviewed in Switzerland agreed that *the absence of a definition of Anti-Ageing products* is one of the reasons why

- it is impossible to estimate the AAM market;
- it is impossible to determine which products or cares that should be included in an estimate of AAM survey;
- it is difficult to decide whether nutritional products, creams or wellness should be included in this market or not.

No data is available on the specific AAM market in Switzerland, neither concerning the production and sales nor concerning consumers' behaviours. As products are easily available on the web (e.g. www.ebay.com), there are a host for private individual and professionals proposing growth hormone, remineralisation gels, skin-care products, beta glucan, and a variety of dietary supplements; a precise figure of the market involved is very difficult to establish except through interview of consumers. The recent study on the health market conducted in Switzerland (Sigrist, 2006) displays a long array of wellness products but also admits the lack of data in AAM consumption or market. The Income and Consumption Surveys, that provide a wide range of information for Switzerland, do not give specific information on anti-ageing products.

While Switzerland has carried out no survey on consumers' most favoured anti-ageing products, a number of surveys have been conducted in the United States to determine the proportion of the population using alternative therapies and anti-ageing products. In 2000, the total U.S. sales for the herbal and specialty supplement industry reached $5.8 billion. One national U.S. survey of more than 2,000 adults, conducted in 1997, found that 42% of Americans of all ages had used at least one type of alternative therapy in the previous year for conditions such as back problems, fatigue, arthritis, high blood pressure, insomnia, depression, and anxiety (Eisenberg et al., 1998). The survey found that 12% used herbal remedies. Other surveys have found that 16 to 18% of Americans used dietary supplements, including amino acids and over-the-counter hormones (Blendon et al., 2001). 1997 estimates indicate that American consumers' of all ages out-of-pocket expenditures for alternative therapies (including herbal products, high-dose vitamins, therapy-specific books and classes, diet products, and professional services) range from $27 billion to $34.4 billion nationally.

Figures related to the AAM market are, however, not consensual. According to the *Freedonia Group*, "U.S. demand for anti-ageing products will rise by 8.7% annually through 2009; at present, the market represents approximately $20 billion. Memory improvement, vision care, and prostate care products will be the leading gains. Chemicals expected to benefit include memory-enhancing neurological and ophthalmic agents, botulinum toxin for wrinkle reduction, and herbal extracts such as lutein, lycopene and black cohosh". The NPD group estimates that the rise will be of 13%. A4M association states that the anti-ageing market is expected to grow to $41.94 billion in 2006. Weintraub (2006) indicates "this industry pulls in $56 billion a year—and that number could rise to $79 billion by 2009".[1]
Very partial data exist at the international level with impressive numbers. In May 2007, the new review "Actif's" launched a specialised magazine on the trends in the dietary supplement segment of the Anti-Ageing market (Actif's, 2007[2]). According to this paper, the slimming segment represents a sales turnover of almost 210 million Euros, the tonics and other complements for energy 104 million Euros and skin and hair 83 million Euros. Emerging segments are products related to sight disorders (25 million Euros, a rise of 1260% during the

1 http://www.businessweek.com/magazine/content/06_12/b3976001.htm
2 Dietary supplements, Actif's Magazine (2007), Vol. 5 :4-10 –distributed at Vitafoods International, Geneva, August 2007.

last four years) and the remineralisation of bones. The authors mentioned that only the products with a real benefit for the consumer and whose nutritional approach is justified will develop. That was the case in the segment of sight disorders: effectiveness studies carried out on the supplements themselves as well as on the ingredients of their formula (e.g. lutein) greatly increased. Out of a total of 885 million Euros, the dietary supplements market is dominated by pharmacies (478 million Euros), specialised networks (120 million), and mail-order firms, internet, and direct sales (120 million).

When considering only senior citizens, the available surveys mentioned, have generally found that as many as 43% of seniors used herbal supplements and 23% used specialty supplements the previous year. It also found that 25% use those products in combination with prescription medication. These surveys have found that consumers use these supplements to maintain overall health, increase energy, improve memory, and prevent and treat serious illnesses, as well as slow the ageing process, among other purposes. Products frequently used by seniors to address ageing concerns in the U.S. include specialty supplements such as chondroitin, DHEA, glucosamine, melatonin, omega-3 fatty acids (fish oil), shark cartilage, and soy proteins, and herbal supplements.

The Anti-Ageing Market Place[3]

- Consumer public is in favour of the anti-ageing healthcare model. *The anti-ageing market place* is one that is demographics-driven: people around the world are getting older. Valued in 2001 at $30 billion worldwide (Dateline NBC, March 21, 2002), the anti-ageing marketplace is projected to reach $42 billion by 2006—representing an average annual growth rate of 8% (Business Communications Company, 2002).
- 60% of Americans age 65+ are pursuing *anti-ageing interventions*—including hormone replacement therapies and dietary supplementation (MSNBC, January 28, 2002).

[3] http://www.worldhealth.net/

- *Dietary supplement sales* in 2000 were $17 billion (Neutrino Business Journal, Nov. 2001). Of these, $1,657 billion were attributed to anti-ageing supplements (Progressive Grocer, vol. 79, no 8, June 2001).
- According to the Robert Wood Foundation, we are witnessing the emergence of the new 'top-tier healthcare consumer'—consumers who are, as a group—college graduates, computer literate, and have an income of $50,000 or more. This group of highly educated high earners is expected to "have the greatest ability to effect change" (Morgan CM, Lewy DL, Marketing to the Mindset of Boomers and their Elders, 2002). They are responsible for reshaping a new healthcare landscape—creating a world in which we all enjoy prolonged life spans, absent of disease and disability, and full of productivity and vitality. This is the new reality that A4M first introduced a decade ago.
- The U.S. based Academy for Anti-Aging Medicine (A4M) unites physicians, health practitioners, scientists, academics and the general public in a spirit to promote cooperative research and application that will yield a scientifically validated, safe, effective, whole-body approach to ageing intervention. A4M presently counts 12,000 members from 70 nations.

(by AAM and A4M founders Klatz and Goldman, 2003)

7.1.2. Future Trends in Anti-Ageing Market

An explosion of sales during the last few years is encouraging future trends in the anti-ageing market. However, it is expected that, as the number of products grow, a selection of actors and a concentration movement will take place. The legislation will also play a role on some decisions such as the possible authorisation for the sale of dietary supplements by pharmacists; the position of insurances and of the Swiss Federal Health Administration regarding reimbursement of some medicines may have an impact on the extension of the market.

An important issue of equality lies in the guarantee of access to health for all. In that perspective, there is no 'AAM access to all', as most of the costs are 'out-

of-the pocket', paid by consumers and create a selection process of who has or does not have access to quality AAM. This is the case in particular for anti-ageing consultations and treatments in private clinics, which charge their clients with the full costs except if they find some illness authorising an intervention. Prices vary according to the clinics. In the United States, Cenegenics clinics charge $2,495 for a health evaluation and about $495 for a monthly treatment. In Switzerland, the Clinic for the prevention of ageing in Genolier offers three kinds of check-ups ranging from CHF 1,500 to 7,200 to be paid by the client. Treatments may rise to CHF 30,000 in the best-known clinics, such as the Clinique La Prairie in Montreux.[4]

REVITALISATION PACKAGE 2007 – Clinique La Prairie, Montreux

Prices in CHF (for 1 person) range between 18,340 and 26,620—for 2 people between 36,080 to 46,040. Prices include 6 nights full board, medical check-up: laboratory tests, chest X-ray, abdominal ultrasound, electrocardiogram; dental check-up; dental panoramic X-ray, complete dental report; revitalisation treatment; consultation and follow-up of the attending physician, nursing care, dietetic advice; 1 consultation with a Beautymed Aesthetician; 1 consultation of personal training; 2 group sessions of aquagym or stretching; access to the fitness centre by appointment, swimming pool, hamam, jacuzzi, and sauna. Not included in the package are: transfer from or to the airport, limousine service, 'à la carte' Beautymed and Thalassomed treatments, and additional consultations with specialists, dental care, additional medical exams (ergometry, mineralometry, mammography, etc.), physiotherapy, and personal expenses.

Given the current costs, needless to say that the main objective of AAM market, both in the United States and elsewhere, is to capture middle- and high-income consumers. However, market laws influence prices, and new approaches are emerging with low-cost AAM and Clinics, as is mentioned elsewhere with the 'Easy Look Clinic' in Geneva.

[4] The data presented is based on clinics visit and documentation during 2007.

In Switzerland, the introduction of TarMed[5] played an interesting role on the access to treatments such as aesthetic surgery, laser, cells, or Botox injections. As interventions reimbursed by TarMed are less profitable than other interventions covered by patients privately, an increasing number of specialists—especially aesthetic surgeons and dermatologists—try to enter the non-reimbursed segment of their speciality of which AAM is part. That trend means a decrease in the prices, but also the emergence of a kind of 'grey market' where some minor interventions are undertaken without control. In 2005, the Swiss Society of Dermatology and Venereology was obliged to publish a notification regarding the danger of using IPLS – Intense Pulse Light System, a new generation of 'laser' intervention, for non-medical use. Other episodes of malpractices, such as irreversible consequences of laser therapy on depigmentation of the skin, were reported by some of our interviewed experts but not verified.

7.2. Socio-Cultural Perspective on AAM

The momentum created by the A4M group has the merit to have triggered a passionate and unprecedented debate on many aspects of ageing: What is ageing, what theories of ageing have been verified or are hypothetical? What do we know about interventions on ageing at the animal ageing level vs. the human ageing level? Never before have so many disciplines embarked on cross-linking and discussing the topic.

7.2.1. The A4M 'Shaking' of an Establishment

When anti-ageing medicine was first proposed in 1993, it was ridiculed and laughed at, and then the debate began to polarise between two extreme discourses as much among the 'anti-agers' as among the 'anti-anti-agers'; the protagonists saying "it is the end of ageing and the beginning of practical immortality" and the opponents saying "ageing is inevitable and irreversible. There is nothing you can do. Don't even try."

In fact, the A4M was created because its founders considered that the gerontological establishment had failed in their mission to prevent the age-

[5] TarMed is Switzerland's new Healthcare-funding Regulation introduced in January 2004. For further information, see http://www.hi-europe.info/files/2004/9958.htm

related diseases and best serve the people at large. Unfortunately, the National Institute of Ageing did not follow up on their primary goal set up in the late 1960s and deviated from their initial goal:

> "A congressmen, one of the founders of the 'National Institute on Aging' (NIA), admitted before dying, that NIA is nothing like it was meant to be. It was meant to be a group of scientists and physicians and sociologists who were all coming together to fight ageing as a disease process and to seek active interventions in the ageing process. He said that shortly after the founding of the NIA, it was taken over by the sociologists and the entire geriatrics, a gerontological system evolved around it that was focused on old age as a normal condition which is not worth fixing or improving outside diseases because it is 'natural'. It became like a religion, like a dogma with no further questioning."
>
> (Dr Klatz
> personal interview conducted for this report, London, September 2006)

The 'Academy of Anti-Aging Medicine' (A4M) came along and started voicing very loudly to the physicians: "We shouldn't be celebrating ageing. We should be fighting tooth and nail against ageing. Because ageing is linked to a disease process, so is it natural? Tuberculosis was natural, polio was natural, the plague was natural. We in A4M are saying that ageing can and should be treated. The degenerative processes of ageing are diseases, ageing *per se* is not a disease, but the pathological processes of ageing that lead to chronic degenerative diseases and death are." (Dr Klatz)

Today A4M has become a fast growing and very visible medical society, not yet recognised by the American Medical Association; nevertheless, it has developed its own way and seems to respond to a need: it delivers certificates of further education and has trained over 50,000 patients around the world. A4M protagonists also declared, very ironically, to be "the only medical society in history where 100% of its members are patients themselves, as no doctor becomes involved in anti-ageing medicine and would not treat himself/herself too." (Klatz, personal interview, 2006)

7.2.2. The AAM Opponent's Responses

On the other side, the opponents have counter-attacked this movement, which was for some a discredit to their work. As is often the case for new scientific fields, an important fight over the legitimacy of AAM has taken place. Debates are especially virulent about 'boundary work' that parallels disputes in many other areas of medicine and science in which rhetorical demarcations are employed to maintain legitimacy and power (Gieryn, 1983). AAM is making its way in the scientific world to find a legitimate place with many challenges and much opposition.

War on Anti-Ageing Medicine

"Leading members of the gerontological community have recently launched a war on anti-ageing medicine, seeking to discredit what they judge to be fraudulent and harmful products and therapies, and to distinguish their research from what they regard as the pseudoscience of the anti-ageing movement. The contemporary war on anti-ageing medicine is largely an attempt by established gerontological researchers to preserve their hard-won scientific and political legitimacy, as well as to maintain and enhance funding for research on the basic biological mechanisms of ageing. First, it recounts the difficult struggle of U.S. biogerontologists to join the scientific mainstream in terms of legitimisation and public funding. Second, it examines how elements of a contemporary anti-ageing movement seem to threaten the hard-won public legitimacy of established gerontological researchers and practitioners. Third, it looks at the "boundary work" responses of the gerontological community to the anti-ageing movement. Finally, it assesses the consequences of the war on anti-ageing medicine to date."

(Binstock, 2003)

As Binstock (2004) points out, the gerontological and geriatric establishment has taken 3 types of approach to discredit anti-ageing medicine:

1. *Redefining anti-ageing or ageing research:* Part of the establishment maintains the legitimacy of research on ageing by inventing new terminology to describe its possible benefits; in a letter to Science, some gerontological researchers debated over the term: "Misuse of the term 'anti-ageing medicine' has led many scientists to shy away from using the term at all, for fear of guilt by association" (de Grey et al., 2002a), while others clearly oppose the term anti-ageing by wanting to replace it: "We should rename the field of ageing medicine in 'longevity medicine' to differentiate it from 'anti-ageing' practitioners and their nostrums." (Butler in ILC, 2001: 64)

2. *Labelling it as 'fraudulent', 'exploiting the ignorance', 'oxymoron', 'fake', 'charlatans', etc.:* This discredit is led by the demographer Olshansky (2004a, 2004b). Some of the examples of the campaign against anti-ageing medicine were:

- A statement of 51 biogerontologists against anti-ageing medicine: In 2002, a position statement was issued by 51 biogerontologists convened by Jay Olshansky and his colleagues to assert that there are no effective anti-ageing measures at present which 'affects the credibility of serious scientific research efforts on ageing'.

- An article by the Scientific American against anti-ageing: An article under the title "No Truth to the Fountain of Youth" was published, written by the same protagonists who launched the statement (Olshansky, Hayflick and Carnes, 2002a).

- An American Association of Retired Persons (AARP) report to 30 million readers: The AARP, one of the strongest lobby of retired people in the world (more than 30 million members), reported in their Bulletin the attempt to discredit the anti-ageing movement (Pope, 2002).

- A prize against anti-ageing medicine: A prize was instituted and publicised by Olshansky presenting two types of 'Silver Fleece Awards' to various anti-ageing organisations and products.

3. *Battling over legitimacy of research on ageing:* "The misleading marketing and the public acceptance of anti-ageing medicine is not only a waste of health dollars; it has also made it far more difficult to inform the public about legitimate

scientific research on ageing and disease." (Scientific American, 13 May 2002[6]) It is not surprising that the anti-ageing medicine movement—spearheaded by the American 'Academy of Anti-Aging Medicine' (A4M)—reacted strongly to the various attacks on anti-ageing medicine:

- *To the 'National Institute on Aging' (NIA):* A4M berated the NIA for its consolidation of power and its "disinformation" campaigns against anti-ageing medicine (Arumainathan, 2003).

- *Law suit for defamation:* A4M has also filed a $120 million lawsuit for defamation and slander that is pending against two of its most ardent gerontological critics.

- *Criticising a lack of 'open mindedness':* Aubrey de Grey, University of Cambridge, has vigorously been promoting SENS (Strategy for Engineering Negligible Senescence) to attain indefinite postponement of ageing (2002b). In a 2005 journal article he took the biogerontological community to task for not maintaining "an open mind" to SENS, and thereby delaying progress and "costing lives" (De Grey, 2005a). Strong response from a group of 28 biogerontologists against what they called "the publicity drawn to ageing research by the SENS/de Grey juggernaut that threatens to drag the public image of research on ageing back into the shadows of 'charlatanry' from which it has only escaped within the past 30 years" (2005b).

The protagonists of A4M also characterised Olshansky as "part of a 'multi-billion dollar gerontological machine' that, without any basis in truth or fact, seeks to discredit tens of thousands of innovative, honest world-class scientists, physicians and health practitioners" and responded to the scientific American position statement point by point and called for a "conspiracy theory". Those attacks are directed to the establishment of gerontologists who carry out the research that could further A4M purposes. The fact is that some researchers in the gerontological field, and especially in the biogerontological establishment, are pursuing exactly what A4M considers as currently validated data (e.g. caloric restriction or stem cells).

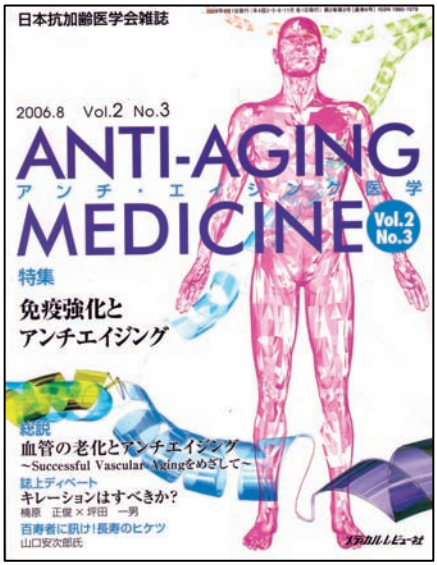
[6] http://www.sciam.com/article.cfm?articleID=00084B01-3655-1CE5-93F6809EC5880000

7.2.3. Japan, an AAM-Friendly Country

Contrary to the situation in the Western world, anti-ageing medicine is well received in Japan. From the many interviews conducted for the report (including the Japanese Longevity Centre, the most renowned universities, ageing specialists and clinics), it became clear that Japan was very keen on the development of anti-ageing research and its potential in clinical applications. Most clinical doctors referred to as experts in regenerative medicine or anti-ageing had followed more than one of the A4M training courses. The first "Anti-ageing International Symposium" took place in June 2006 in Tokyo bringing together scientists, politicians, pharmaceutical companies, private sector, patients and A4M.[7] Following that congress, two movements of AAM emerged and developed: on the one hand, the scientists and the biogerontologists who do not adhere to A4M in Japan and want to distance themselves from non-scientific approaches, have created their own consortium of anti-ageing medicine; on the other hand, the A4M-supported movement, which proceeds with their own consortium and organises or supports events, such as "Total Anti-Ageing in Japan: the 1st World Anti-Ageing Congress & Exposition in Japan" in 2007[8].

Contrary to the situation in United States, the Japanese who resist A4M have adopted the term 'anti-ageing medicine' for their scientific work, be it at the Tokyo Metropolitan Institute of Gerontology Research for Biomolecular Biomarker (Dr Shirasawa) or at the Keio University School of Medicine Department of Ophthalmology (Dr Tsubota) or other academic institutions. Those researchers, professor of medicine, chairs of universities, have created successfully the first Japanese peered-reviewed "Journal of anti-ageing medicine" in 2006. The editorial board is composed of 21 eminent scientists from different medical disciplines:

[7] http://www.imagina.jp/aiset
[8] http://www.worldhealth.jp/english/



From the data and the interviews conducted, the anti-ageing medicine concept and search for effective interventions and boosting performance does not pose a problem in Japan. Rather, it corresponds to a cultural trait: the desire to be a key player in the highly competitive arena of technological developments. Two examples portray this attitude to research on anti-ageing and peak body performance:

Example 1: Competition for Age Record in Peak Performance

Japanese Competition for Age Records in Climbing Mount Everest[9]

Yuichiro Miura, a Japanese man who just turned 75, belongs to a cluster of greying Japanese climbers who since 2002 passed among themselves the title of 'oldest person to conquer the tallest peak in the world': Toshio Yamamoto started the string of Japanese victories by scaling the peak in 2000 at 63 years. In 2001, the American Sherman Bull reached the

[9] Associated Press article (14 Oct. 2007) "Everest beckons more Japanese seniors" by Chisaki Watanabe.

summit at 64. Tomiyasu Ishikawa, then 65, took the title in 2002. In the same year, Tamae Watanabe at age 63 was the oldest woman on the Everest. Miura won the distinction in 2003, at 70, but was eclipsed by fellow Japanese climber Takao Arayama, who scaled the peak in 2006, just three days older than Miura was when he did it. Katsusuke Yanagisawa took the crown this year at age 71 years and 63 days. Now Miura wants to reach the top again and break the record.

Some attribute the prevalence of Japanese adventurers to the same factors that make them live increasingly longer: a diet heavy of vegetables and fish, excellent health care and trim physiques. “Overall, the elderly have more vitality than before and their performance in sports is also improving,” said Takuji Shirasawa, a specialist on ageing at the Tokyo Metropolitan Institute of Gerontology who advises Miura. He is in excellent shape as a test before his 2003 climb proved him to be as fit as a 39-year-old man, according to Masayoshi Yamamoto, exercise physiology professor at the National Institute of Fitness and Sports in Kanoya in south-western Japan. Staying active into old age is in his genes. His father made headlines three years ago when he skied down Mont-Blanc at the age of 99. He died last year aged 101.

The socio-economic factor also plays a decisive role in extreme performance by the elderly. The increase of commercial expeditions starting in the early 1990s allowed inexperienced but rich climbers to reach the summit. The climbing techniques have changed (e.g. use of oxygen, pace of climbing, technology, etc.). Money brings world-class equipment, expert assistance on the mountain, and state-of-the-art training. Miura's climb was estimated at around $1.7 million spanning three years to 2008. The effort is supported by corporate giants including *Toyota Corp.* and *Toshiba Corp.* Miura has built a $260,000 low-oxygen room inside his Tokyo home to help him acclimatise to the thin air.

Miura says setting a record isn't all that important, since someone else will surely come along and break it. Instead, he said: “It's about discovering what I can do. It's a tough but wonderful thing to get to the peak when you are past 70, I hope to send the message that we have the potential for many things in this ageing society.”

Example 2: Robot-Friendly Society

In 1927/28, Japan was the first country in the world to produced a real robot Gakutensoku conceived by the biologist Nishimura Makoto, that could open eyes and mouth, smile, turn his head, use a pen with compressed air and tubes. Since then the country has always been fascinated by robot research and development. Japan produced world success miniature robots such as Tamagochi, Furby, Aibo, Papero, etc. The government has implemented strong policies to further encourage the creation of robots. Japan's Ministry of Economy, Trade and Industry (METI) announces each year the top ten list of finalists for the Robot Award. The ten robots selected from more than hundred applications fall into four categories—service robots, industrial robots, public sector robots, and small- to medium-sized venture robots.[10]

Robots are particularly interesting for the government as a solution to respond to the record-breaking proportion of older persons and numbers of centenarians (32,295 centenarians in October 2007 – see box below). Given the policy on immigration wants to keep a steady low rate of immigrant workers, the government strongly encourages innovation through financial incentives and promotes a technology-friendly society where robots will serve as carers and company pets for elderly people and children and are believed to improve considerably the quality of life.

Tim Hornyak in his essay "Loving the Machine: the Art and Science of Japanese Robots" (2006), explains the fascination of Japanese people for robots and their beliefs that robots are not in-animated and lifeless objects but entities with their own personalities and as such are friends and partners of human beings. This belief is engrained in all generations and transmitted by religion which makes little difference between the animated and the in-animated world—according to certain belief systems natural phenomena (waterfalls) or objects created by man (sword of the Samurai) are inhabited by a 'spirit'. Many traditions and rituals of this kind exist. Masahiro Mori, professor at the University of Science and Technology in Tokyo also refers to the link between robots and spirituality in his book "Buddha in the Robot" (1981). Robots are the quest for an ancestral wisdom where there is no slave and master in the link between man and machine. They are a mutually dependant entity. Hornyak stressed that in Japan the relation between man and machine, between new technology and the

[10] http://www.pinktentacle.com/tag/meti

population is not antagonist. Contrary to the Western world, traumatised by industrial revolutions and social disorders, Japan has embarked on a rapid modernisation programme since the end of the 19th century to survive the invaders. According to Hornyak, the Japanese have always considered the machines as their saviours. They have even attributed domestic animal names to their airplanes and to industrial robots, which reflect the relation of robot/technology-men partnership (2006).

Japan Health, Labour and Welfare Ministry, September 2007: "Centenarians to exceed 30,000 for first time in Japan"[11]

The Health, Labour and Welfare Ministry of Japan, announced a record of 32,295 centenarians in September 2007, up 3,900 in a year.

Women continue to make up the vast majority of centenarians, accounting for 85.7%, the second-highest on record since the 86.9% recorded in 1963.

There is a record 27,682 centenarian women, up 3,437 from last year, and a record 4,613 centenarian men, up by 463. On September 1, 2007, the ministry tallied the number of people in the nation's 47 prefectures who are already or expected to be centenarians by the end of the month.

The oldest man is Tomoji Tanabe of Miyakonojo, Miyazaki Prefecture, who will turn 112 during the month. In January 2007, Tanabe was listed as the world's oldest male by the Guinness Book of Records and received his certificate in June. The oldest woman is Tsuneyo Toyonaga of Tano, Kochi Prefecture, who is 113. By prefecture, Okinawa has the largest proportion of centenarians with 57.89 per 100,000 people, maintaining the top position for the 35th straight year.

The ministry also said that a record 17,778 people will reach 100 by the end of the 2007 fiscal year through March 31, 2008. That's up by about 2,400 from the previous fiscal year.

There were 153 centenarians in Japan in 1963. But that eventually rose to 1,000 in 1981 and passed 10,000 in 1998. The numbers for centenarian men have set records for 27 consecutive years, while those for the women have broken records for 37 years in a row.

[11] The Japan Times article (15 Sept. 2007) "Centenarians in Japan soon to exceed 30,000 for first time", Kyodo News – http://search.japantimes.co.jp/cgi-bin/nn20070915a4.html

7.3. Ethical Perspective

History shows how developments in biomedical science—like cloning, genetically modified organisms, engineered humans—can fascinate society and lead them to believe the 'impossible' is a possible future. Much debate and discussion has taken place between scientists about the science of longevity and ageing and anti-ageing, but very little analysis exists of the societal and ethical consequences that might ensue if such interventions are achieved. This chapter presents three approaches; first, the points of view of international ageing experts met during the development of the project; second, some statements published by philosophers and ethicists; and in a third the position of Dr Leslie Olson who kindly reacted to a first draft of this study.

7.3.1. Ethical Issues from International Ageing Experts

Among the experts we consulted, very contrasting opinions about anti-ageing medicine guided this report's concern on some ethical problems. Those who were in favour did not see any ethical obstacle to the development of anti-ageing medicine whereas those who were against it presented a wide range of ethical problems.

The arguments of the first group—the 'pro-AAM'—came clearly came from the biogerontological field; here some experts even stated that it was "unethical not to support the development of interventions and preventions that would potentially slow down, arrest, or reverse the process of ageing". The second group—the 'Anti-AAM'—a majority of geriatricians, saw ethical problems in the AAM movement (see listing of arguments in table 11a below) mainly for the following four reasons:

i.) *Discrimination*: AAM stigmatises ageing

ii.) *Absence of data:* lack of "scientific evidence on AAM", which leads to a 'high-risk medicine'

iii.) *Abuse and misuse:* AAM is a fraudulent market taking advantage of the illusion of 'immortality' and the 'fountain of youth'

iv.) *Societal dilemma:* danger of creating a society with a dichotomy between those who will age naturally as today, and those who do not want to age and will want to stay young to the end, thus resenting old age, but most importantly the latter could also

promote a movement resenting everyone 'looking old' and 'being age-handicapped'

Along these line other 'anti-AAM geriatricians' such as Dr Robert Butler who created the International Longevity Centre in New York, have consistently insisted on ethical arguments against anti-ageing: "The very concept of 'anti-ageing medicine' goes against the last fifty years of work in gerontology, devoted essentially to differentiating normative and natural ageing processes from diseases such as arteriosclerosis. The idea of 'anti-ageing' also promotes and reinforces ageism. It puts a profoundly negative connotation on the very occurrence of ageing, emphasising its negative and depleting aspects. For example, this concept (anti-ageing) denies all that is enriching and positive about ageing in the psychosocial sphere" (Butler, ILC, 2001).

Table 11a: The Four Main Ethical Issues Among Interviewed Experts

1. *Stigmatisation of age* that leads to 'gerontophobia' and 'ageism':

"Anti-aged people might become the new standard for successful ageing—the frail elderly will then become the losers." (geriatrician, Switzerland)

2. *Principle of maleficience and evidence-based therapy*:

"AAM opens the door to many kinds of abuses, mainly because it is looking for results which cannot be obtained. Based on the fact that no one wishes to age, it is logical that individuals with no knowledge about ageing or medicine, about efficiency or side effects/risks, will easily tend to choose such new ways in fighting ageing. Despite extensive information, it could nevertheless be accepted as legal by a judge in the case of a trial." (biologist and endocrinologist, Spain)

3. *Market enhancing inequality* – No access to all:

"Currently, only persons who can afford private consultations have access to anti-ageing services. This fact itself causes an ethical dilemma. If anti-ageing products are beneficial, which I doubt, they should become available to all." (geriatrician, Switzerland)

4. *Medicalisation of ageing* – Inequality in resource allocation:

"There is an ethical issue if anti-ageing medicine turns 'age' into a disease rather than a natural (and in many ways necessary and desirable) part of life [and if] it uses resources in such a way as to make essential health care unavailable to other people in society (a violation of the 'fair inning' concept)." (lawyer, Switzerland)

Even biogerontologist Leonard Hayflick—regarded by many in the field as having laid the groundwork for contemporary research advances in molecular mechanisms of ageing (Shay and Wright, 2000)—has long feared the societal implications of slowing or arresting the ageing process such as worldwide overpopulation and its consequences (Hayflick, 1998, 2000). However, he agrees with most other biogerontologists and gerontologists in regarding as highly desirable the compression of morbidity as long as it does not involve extending average life expectancy beyond 100 years.

7.3.2. Ethical Issues Debated Among Ethicists and Philosophers

Among the experts in ethics, only a few have addressed the ethical issues of anti-ageing medicine. A few ethicists, but more so bioethicists, have taken clear positions distinguishing between those who see no objections and those who see many reasons for concern in anti-ageing medicine and anti-ageing concepts. Although it is not always possible to distinguish between pro- and anti-AAM ethicists, a short review of the literature can offer the synthetic description of the positions against or for AAM.

Table 11b: The Ethical Issues Debated

Statements of the 'no objections' ethicists	**Statements of the 'objectors'**
John Harris, bioethicist, United Kingdom, sees no coherent ethical objections and thinks that efforts to attain prolongevity should go forward (Harris, 2002; Harris and Horn, 2002).	*Daniel Callahan*, American bioethicist, published in 1987 a book that proposed health care rationing for older people in a context of population ageing. He qualified the growing contemporary population of older Americans as a "social threat" and "a demographic, economic, and medical avalanche […]

	that could ultimately do great harm" (Callahan, 1987: 23).
Michael Fossel, editor of the Journal of Anti-Ageing Medicine, embraces the "promise of a time when we will live longer and much healthier lives—of one hundred, two hundred, possibly five hundred years." (Fossel, 1996:1)	For *Alex Mauron*, professor of bioethics at the University of Geneva, the most efficient anti-ageing medicine already exists, it is to "be born in an affluent, well-educated family in a Western country, grow up to be a hard-working, successful entrepreneur, and above all, be convinced that the merit of your success is all yours, and that the un-successful have only themselves to blame." (Mauron, 2005)
Charles McConnel, professor of health economics at the University of Texas: "Given the constraints and opportunity costs asso-ciated with the production and consumption of anti-ageing products and services, health economics offer a clear conceptual and theoretical framework within which the potential behaviour of economic agents, be they consumers or producers, can be evaluated and outcomes better anticipated. The health production model, which incor-porates disease as a random event and views the consumer of health care as one who is investing in additional productive days of life as well as in the enjoyment of those additional days, seems appropriate since it accommodates investments in both the quantity and quality of life." (McConnel, 2004)	*Leon Kass*, humanist philosopher and chairman of the U.S. President's Council on Bioethics: "The finitude of human life is a blessing for every human individual, whether he knows it or not", "to covet a prolonged life span for ourselves is both a sign and a cause of our failure to open ourselves to […] any higher purpose". Kass even condemns compression of morbidity: "[I]t is highly likely that even a modest prolongation of life with vigour or even only a preservation of youthfulness with no increase in longevity would make death less acceptable and exacer-bate the desire to keep pushing it away." (Kass, 1985; Kass, 2001: 20 and 316)
Arthur Caplan, professor of bioethics at Pennsylvania University: "We do not know enough about ageing to know if any of these interventions can deliver a longer life much less immortality. But, should this research be	*Jürgen Habermas*, a philosopher, opposed and launched an attack against "eugenic" modifications of human nature, based on the "ethics of the species" (Habermas, 2001, 2003). For

stopped? […] I maintain that research on slowing and even 'curing' ageing should have greater priority in research budgets than it now does." (Caplan, 2004)	Habermas, certain technical intervenetions in human natures, especially in the line of human genetic engineering and pre-implantation genetic diagnosis, undermine the very possibility of human freedom and function, preserving the species from the risk to lose individual self-determination.
Julian Savulescu, professor of practical ethics at the University of Oxford, is concerned puts patient's rights at the centre: "A doctors' conscience has little place in the delivery of modern medical care. What should be provided to patients is defined by the law and consideration of the just distribution of finite medical resources, which requires a reasonable conception of the patient's good and the patient's informed desires. If people are not prepared to offer legally permitted, efficient, and beneficial care to a patient because it conflicts with their values, they should not be doctors. Doctors should not offer partial medical services or partially discharge their obligations to care for their patients. […] Imagine an intensive care doctor refusing to treat people over the age of 70 because he believes such patients have had a fair innings. This is a plausible moral view (Harris, 1985),but it would be inappropriate for him to conscientiously object to delivering such services if society has deemed patients are entitled to treatment" (Savulescu , 2006)	

Tom Mackey from the Georgetown University Law Center in Washington DC defends six ethical arguments against AAM and four in favour of AA:

Ethical arguments in favour of AAM	**Ethical arguments against AAM**
1) *Beneficence:* duties to maintain health and prevent disease and death; 2) *Efficiency:* slowing down ageing would reduce the rates for all of the most common causes of death in developed societies; 3) *Limited autonomy:* freedom to purchase AAM substances that may or may not work, so long as they are not harmful; 4) *Improved quality of life:* more active, healthier, and wiser (two propositions supporting this argument—that anti-ageing medicine would allow for a longer, more active, healthier, and fuller life and that wisdom comes from experience, not from senescence).	1) *Inequity:* the poor die young by the millions, while the rich refuse to age; 2) *Denying ageing's immutability*; 3) *Dominating nature*, altering and commodifying ourselves; 4) *Overpopulation:* carrying capacity concerns and the rights of future people to be born; 5) *Ennui*: with no natural deadline, life itself outlives its value; 6) *Ageism:* prejudice and discrimination because of age difference, either against the old or the young.

According to Mackey (2003), the arguments in favour of AAM are found to be more compelling than the arguments against it, but he suggests the recommendation that AAM should be funded and regulated in ways that facilitate its potential both to reduce the incidence and prevalence of many diseases and to allow for longer, fuller, and more meaningful lives. As Fischer and Hill (2004) note it, current therapies carry many doubts about the safety and effectiveness of AAM, which makes its practice with the prescription of anti-ageing therapies a challenging issue from both a legal and ethical perspective. Finally, although the practice of AAM is not directly recognised and regulated by legislation, both anti-ageing treatments and practice are slowly emerging in state and federal legislation of evolving complementary and alternative medicine.

From the different point of views, it appears clearly that the ethicists do not agree among themselves. Depending on which point of view on science evolution and life one takes, AAM will be discredited or welcomed. The fact that AAM is a fast growing field and is linked to people's desire makes it even more controversial. The ethical discussion will evolve in parallel with the innovations, the research evidence, the information and the practices, but also with human behaviour on the matter. The debate is not closed but is definitely open and needed.

7.3.3. Some ethical challenges of AAM: a Moderate View

Markus Zimmermann-Acklin, ethicist at the University of Luzern in Switzerland

Three areas should be considered in the ethical debate of anti-ageing medicine: (i) the *normative* questions on rights and duties, (ii) the questions of *evaluation:* what is a good or flourishing life, and (iii) the *hermeneutical* questions concerning the cultural perspective, e.g. meanings of ageing, disease and health. It is important to be aware of the different areas of discussion in order to avoid misunderstandings around the ethical debate on AAM. Here are a few of its key points:

- *Normative questions*: In this area it is essential to think both about justice and possible consequences of any new practice. There are no relevant arguments concerning rights or duties as to how ageing should be considered. In contrast a very important point is equity and equality: If there are any new possibilities of increasing quality of life by AAM, should they be available to everyone? Who will pay for them? Furthermore, we have to consider possible outcomes of AAM, especially as to its potential to increase the already existing forms of age discrimination.
- *Evaluative questions*: Is there something like a 'natural life span' which we should respect (Daniel Callahan)? What about the current tendency to forget about finitude, suffering and dying as normal human experiences? We have to consider different answers to the question of the meaning of ageing, suffering, health and disease. Concepts of a 'good life' are always context and culture-specific and difficult to discuss in the presence of controversy, yet the debate is necessary as cultural or ethical concepts are never neutral.
- *Hermeneutical questions*: The understanding and meaning of ageing, illness, normality and abnormality; the nature of human life is viewed differently from culture to culture. Thus the issue of illness or better health in ageing cannot be addressed without considering the cultural context of different societies, even if 'objective' sciences claim the contrary.

The clarification of the borderline between reasonable or beneficial medical treatment and luxury medicine is also important for AAM, because a decision is

required on what should be paid by social insurances or by the patient himself/herself. In this respect the ethical debate on AAM which leads to the issue of rationing of health care and justice.

From the public health perspective, preventive measures for better and healthier ageing should be encouraged, as long as personal freedom to choose one's lifestyle is not reduced. It is important to keep in mind that we will not save medical expenditures by extending the average life span. The older the human being, the greater the probability of chronic disease or the need for care. At the end of the road there remains the inevitably expensive last period in life, the dying process, despite all advances in health care generally and in AAM in particular.

7.3.4. Ethical Aspects of Anti-Ageing Science – A Point of View

Dr Leslie G. Olson, WHO Research Ethics Committee member and WHO technical consultant, Fellow of the Royal Australasian College of Physicians

Two main ethical issues arise in relation to anti-ageing science: 1) the first is a matter of *principle:* whether it is wise or proper to (attempt to) prevent or delay natural death indefinitively, 2) the second is a matter of *practicality:* how to respond to research intended to alter the course of life in reducing the impact of ageing, and how to regulate the market and the use of whatever procedures or pharmaceuticals products, as well as the research. These are quite independent questions, and it is unfortunate that the wisdom of trying to eliminate ageing, which is a remote possibility, has received so much more attention than the other question, which requires an immediate answer.

Under the umbrella of anti-ageing research several models of what could be considered as progress can be distinguished as they have rather different implications. The first is 'healthy ageing': a conservative approach focused on improving the functional capacity and quality of life of the aged (WHO, 2002b). The intent is to compress morbidity and disability into a short period immediately preceding death rather than extending the life span. This is usually assumed to be an obviously good thing, although, for reasons which hopefully will become clear, the ethical argument will be detailed below. The second approach is much more radical: to eliminate one by one all potential causes of disability and death, so that the healthy life span is extended two- or threefold. The third is even more radical, proposing that ageing itself can be eliminated so

that humans will be ageless and live indefinitely. Most commentators use 'anti-ageing science' to refer only to the two first variants.

There is, at present, less true 'anti-ageing science' than the controversy would suggest. Most of the claims which give rise to conflict concern the results of experiments that anti-ageing researchers like to imagine but which, for purely technical reasons, they have no immediate prospect of undertaking. Alex Mauron has gone so far as to suggest that the debate about anti-ageing research is not about death and ageing at all, but just another battle in the 'culture wars'—the latest 'symbolic crusade' against the possibility of socially transformative science and the advance of non-religious values (Mauron, 2005). There is certainly much truth in this outlook: both sides conduct the debates more as a Nietzschean "play of forces" than as a meeting of minds (Deleuze and Guattari, 2004; MacIntyre, 1998). However, there is some ethical substance to the issues raised by anti-ageing research, and that ethical considerations can point the way to an appropriate regulatory policy.

The ethics of outright charlatanism will not be discussed. Consumers are entitled to receive their government's protection from charlatans, but there is nothing new or special about anti-ageing charlatans.

A further issue that should be mentioned, without going into details, is that of 'time horizons' when discussing the ethical aspects of speculative futures. If anti-ageing science succeeds in its project, it will only be after a period of trial and error, dead ends and failures, which is very unlikely to last less than several decades. Nearly all the discussion of the ethics of anti-ageing science, however, pre-supposes the success of the anti-ageing project, and does not concern the ethics of anti-ageing science during the period of failure. A strong case can be made to consider this is a mistake, and that any ethical concern should be of paramount importance for the near future, so that the ethics of failure also become an important concern.

Is it at all possible that anti-ageing science could, eventually, achieve its aims? A good deal of progress in extending average life expectancy at birth has already been made; anti-ageing researchers often treat their own visions of the future as a simple continuations of what has been achieved in the past. This is misleading. Increase in life expectancy at birth is a fact mainly because infants no longer die as previously, but the maximum life span has increased little despite the doubling of life expectancy at birth. There are few prospects in rich

countries for further improvement in the factors that lead to life expectancy at birth doubling—indeed, some demographers predict that life expectancy will fall over the next 50 years because improved nutrition has caused such widespread overnutrition.[12] The factors that lead to increased life expectancy at birth were not targeted interventions but can be recognised as causes of reduced disease only in retrospect. Some of them, like improved nutrition, are two-edged swords: it was shown seventy years ago that if a balanced diet is assured, life expectancy can be increased about 30% by severe calorie restriction (McCay et al., 1935).

Targeted primary prevention of specific diseases such as coronary artery disease has not produced survival gains (indeed, some of the treatments promoted, such as estrogens, have turned out to promote coronary artery disease instead). The reason may have been inappropriate treatments, in which case research leading to better treatments should solve the problem, but the reason may also be the so-called paradox of prevention: "the cause of cases is not necessarily the same as the cause of incidence" (Rose, 1985). Another common mistake is to suppose that because 20% of people die of cancer, curing cancer will reduce mortality by 20%, and thus eliminating by a 100% the causes of current mortality will reduce mortality by 100%. The mistake lies in forgetting that causes of death are mutually exclusive but pathological processes are not: dying of cancer this year means you cannot die of coronary artery disease next year, but if the cancer were cured this year your coronary artery disease would still kill you next year. As the rise of Alzheimer's disease with population ageing shows, pathological processes, formerly inconspicuous, may lie in wait for the ageing and prevent any marked increase in life expectancy when the diseases that kill us now can be cured. For this reason, it is speculation to assert that we can radically prolong life by eliminating one by one the diseases people currently die of.

The 'healthy ageing' project is both the most likely to succeed and ethically the least problematic. It does not raise issues over the propriety of interfering with aspects of human life considered to be fundamental, and it is unlikely that the research be conducted unethically. The reasons for this attitude will be reviewed, as some of them also apply to the more radical variants of anti-ageing science.

[12] "No community has managed to eliminate under-nutrition without causing over-nutrition"; see Berrios et al., 1997.

Most commentators agree that there is no ethical reason to reject the opportunities to mitigate suffering or disability made available by human ingenuity. No one suggests, for example, that it is wrong to use spectacles to correct myopia, nor is there any ethical reason to reject an opportunity to relieve disability just because that disability is more common in older persons than in the young (no one suggests that it is wrong to use spectacles to correct presbyopia). Further, the Catholic Church and Islamic tradition both assert a *prima facie* obligation to seek and accept care, and equate death caused by refusing straightforward effective treatment with murder or suicide (Tettamanzi, 2002; Sachedina, 2005). There are exceptions to the view that using the product of human ingenuity is always legitimate, but relate to specific prohibitions of a method (e.g. Jehovah's Witnesses and blood transfusion), or to prohibitions against an aim (e.g. Catholics and contraception, which differs from the Jehovah's Witness case because the use of estrogens and progesterone for non-contraceptive purposes is not forbidden).

So it is hard to see that there will be any in-principle ethical objection to the 'healthy ageing' project, at least if it is conceived as the WHO document quoted above conceived it. It is *very* important to remember that 'healthy ageing' understood in this way means, not only making the aged more fit for the world, but also making the world more fit for the aged. This is important because while reducing disability which is almost certainly an achievable goal within the lives of people who are now adults, eliminating disability, even for the very rich, is almost certainly not. There would be ethical problems with an approach that reduced morbidity but increased the marginalisation of those who continued to suffer ill-health—a likely outcome, all other things being equal, because the disabled would be fewer and less politically influential. A more serious problem would arise if reducing the morbidity associated with ageing left those who had not benefited not only marginalised but stigmatised. The prejudices that in many communities worsen the disability caused by age-related ill-health would not disappear when age-related illness became uncommon. They might, like many prejudices against declining minorities and against those who suffer from illnesses, be perceived as preventable or get worse. Nevertheless, there is no reason we cannot both suffer less and behave better, so that the risks of marginalisation and stigmatisation are not a reason to stop anti-ageing research.

A major ethical problem with current medical care is inequity of access, and since it is unlikely that new anti-ageing treatments will be cheap, inequity would

get worse if effective anti-ageing treatments were developed. Anti-ageing treatments, like anti-retroviral treatment, would be available to the rich more easily than to the less rich and not at all to the poor. That precisely is a reason to remove inequities, but not a reason to stop anti-ageing research, any more than it is been taken to be a reason to stop research on anti-retroviral treatment. (It is true that anti-ageing science often appears to be indifferent to inequity (McConnel and Turner, 2005), but it should be considered as a different issue to be addressed later).

Research directed at making ageing more comfortable is research for rich people not only because it will be imperative to be rich to afford the treatments but also because rich people are far more likely to get old enough to need them. Thus, anti-ageing research would not only worsen inequity in case of success, it is inequitable whether it succeeds or not, like all the other examples of disproportionate resource use by rich people. This is an argument for giving anti-ageing research a low priority given the available resources, but not an argument to considering anti-ageing research wrong *per se*.

A broader objection to the anti-ageing project—an objection to be considered in isolation—is a concern that the motivation for seeking to eliminate disability is that people are valued because of what they can do, not because of what they are. The problem lies in the fact that the standard of worth is capacity and inevitably some people are worth more than others. In relation to projects aimed at eliminating hereditary disease, it is argued that apparently benign aims such as “correcting genetic defects” are ethically questionable because they imply that the people concerned are “defective” (Buchanan and al., 2000), and the same argument could be made about the disabilities currently associated with ageing. It is certainly true that the difference between saying “it is a problem that people have disabilities”, and saying “people who have disabilities are a problem” is not universally respected (Sereny, 1974). Those who make this argument advance an alternative: that we should simply value each person more, and not look for a reason to value them more by increasing what they can do (Oe, 1996). There are two responses to this argument: the first is that the ethical stance of healthy ageing is not to value persons only in so far as they can do things useful to others, but to value the person and, independently, to value what they can do (Oe, 1996). The second response is that a person whose disability has been reduced is not benefited less because the motivation of those who helped her was shameful. For these reasons, arguments about the

habilist prejudice inherent in disability reduction provide good reasons to stop efforts to reduce disability.

In practice, the healthy ageing project will not be marked off from current medical practice or from current biomedical research. The testing and use of cholinesterase inhibitors for Alzheimer's disease, for example, has not caused any new or unique ethical or scientific problem, and there is no reason to expect that other treatments for the diseases of ageing would be different if they were developed in a similar way. The standards of experimental design, of ethical conduct and of regulatory review that apply to any other biomedical research can apply just as well to new such as to old healthy ageing research.

Indeed, healthy ageing research should not be seen as different or discussed apart from general medical research, because it is of the highest importance that technical and ethical standards are not compromised or whittled away by allowing a culture of exceptionalism to develop around healthy ageing research, as happened for a time with HIV/AIDS research. In particular, it must be underlined that 'evidence of efficacy' can be provided only by large, well-designed randomised controlled trials using non-surrogate outcome measures.

These arguments have been presented for the ethical appropriateness of the healthy ageing project as they apply equally to that variant of anti-ageing science which supposes that life span can be markedly extended by curing causes of death one by one. It is only when we have prevented or cured cancer, coronary artery disease, Alzheimer's disease and the rest that we can find out whether human life span is, for the time being, limited by the occurrence of disease or is determined by ageing processes and unrelated to specific diseases. However, no one presumably would say that it is unethical to treat or cure cancer or Alzheimer's disease, whatever their view on extending life expectancy that could follow.

Anti-ageing research of all types would cause special problems for research regulation if the experiments and trials required were not set up to follow the rules of ordinary biomedical science. Although many of the scientists associated with radical anti-ageing projects have established reputations in other fields of research, and papers about anti-ageing research are published in ordinary academic journals, anti-ageing projects are often presented in terms that suggest an approach quite different from that normally associated with science. For example, Robert Freitas has written that:

> "Theoretical designs for artificial red blood cells (respirocytes) and artificial white blood cells (microbivores) suggest typical performance improvements of 100 to 1000-fold over natural biological systems. A heavy infusion of respirocytes would allow you to survive four hours without breathing, as during a drowning accident or a heart attack. Injecting a few cc's of microbivores would clear a bloodborne bacterial infection in minutes to hours rather than taking weeks to months using present-day antibiotics. Artificial platelets could staunch bleeding in seconds. Tissue-repair nanorobots could selectively dissolve cancerous tumors or rebuild wounded flesh in minutes or hours. Chromosome replacement therapy will allow us to replace our old worn-out genes with new digitally-correct chromosome copies installed in every tissue cell of our bodies. Such therapies will eliminate all genetic diseases and reverse other accumulated defects that lead to ageing, augmenting human health span at least tenfold."
>
> (www.foresight.org/nano/RobFreitas.html)

This is a curious narrative from a biomedical science point of view: its author is careless about matters of fact (antibiotics do not take "weeks to months" to clear blood-borne infections) and inconvenient details (exactly how will people get infusions of respirocytes "during a drowning accident"?). He borrows his narrative style from television advertisements and his metaphors from computing ("… new digitally-correct chromosome copies installed in every tissue cell …").[13] Despite the magnificence of the technical achievements advertised, the narrative's imagined medical landscape is strangely ramshackle: chromosome treatment is going to eliminate disease, but people will still have heart attacks and need "respirocytes" and develop cancer and need "tissue-repair nanorobots". The problem is not that this is an unethical goal, but that it is hard to see the ethical principles of independent oversight, balancing risks and reasonably anticipated benefit, and informed consent being grafted easily onto this narrative.

The most serious ethical problems are raised by the most radical version of anti-ageing science: "engineered negligible senescence", or the cure for ageing

[13] The metaphor is re-installing a computer's operating system: "It's a big job, but it can cure Windows' creeping decrepitude" – www.pcworld.com/article/id,111652-page,1/article.html, accessed on 14 July 2007.

(De Grey, 2005a). Not everyone can see that those questions are worth discussing: “Ageing really is barbaric. It shouldn’t be allowed. I don’t need an ethical argument. I don’t need any argument […] To let people die is bad.” (De Grey, 2005b) Since some people still insist on an argument it is pointed out that anyone who thinks it is a good idea to die is free to do so, and when to this it is added that wanting to die creates no right to prevent other people from living, the argument in favour of anti-ageing research is held to be complete.

That is a plausible enough argument for allowing people to do anti-ageing research, but it is not an argument for the view that succeeding in that research and eliminating ageing would be a good thing. The only developed ethical argument anti-ageing researchers have presented has allowed progress in favour of *that* proposition which is based on the premise that all human lives are equally valuable, implying the conclusion that all human deaths are equally to be deplored. So, Freitas has written:

> “Even the most widely recognised greatest disasters in human history pale in comparison to natural death. For example, the typhoon that struck Bangladesh in 1970 washed away a million lives. In 1222 AD, Genghis Khan burned the Persian city of Herat to the ground. It took his Mongol horde an entire week to slaughter the 1.6 million inhabitants. The Plague took 15 million per year, World War II 9 million per year, for half a decade each. The worldwide influenza pandemic of 1918 exterminated around 22 million people—not even half the annual casualties from natural death. But natural death took 52 million lives last year. We can only conclude that natural death is measurably the greatest catastrophe humankind has ever faced.”
>
> (www.foresight.org/nano/RobFreitas.html)

This strikes most people as strange, because most people think instinctively that natural death, especially at an advanced age, is different in an important way from being murdered by Genghis Khan. A number of eminent conservative ethical and political writers have formalised this popular response: “… ageing and senescence are both natural processes and, as such, intrinsically good things” (2005). However, as Caplan (2005) and Mauron (2005) point out, attempts to clarify what is meant by “natural” and to establish that naturalness is ethically relevant turn out to be remarkably thin and unconvincing. No argument

has been advanced able to show that saying that death is natural and for that reason ought not to be interfered with, is any different to saying that powered flight and votes for women are unnatural and ought not to be allowed.

De Grey has pointed out that the natural death argument is wrong even on its own terms (De Grey, 2005a). Our instinctive feeling and formal arguments alike are based on the fact that old people have less expectancy of further life but so do children in Sierra Leone, and their deaths are not for this reason regarded as unimportant. Of course, the low life expectancy of children in Sierra Leone is contingent and correctable, and once vaccine-preventable infections, malnutrition, HIV/AIDS and so on are taken out of the equation, children in Sierra Leone have the same life expectancy as children elsewhere. But, once ageing is taken out of the equation, so do 100 year olds, and, once ageing is cured, preventing the death of a 100-year-old is no different from preventing the death of a child. A life has been saved, all lives have the same expectancy of further life with unimpaired vigour, and so all lives are of equal value. It is true that "taking ageing out of the equation" is easier said than done and we do not know whether we will succeed, but taking vaccine-preventable infections, malnutrition and HIV/AIDS out of the equation in Sierra Leone is also easier said than done, and we do not know whether we will succeed.

On this point the advocates of anti-ageing science have a convincing argument, and Caplan and Mauron are right in saying that anti-ageing research cannot be objected to on the ground that it is unnatural.

The argument that all lives are of equal value depends on the assumption, of course, that anti-ageing research will (not "might") take ageing out of the equation by curing it. To make this come true anti-ageing research must not only succeed, but succeed perfectly, so that ageing is abolished and not merely slowed or attenuated. At least some partial success in the anti-ageing enterprise—preventing death without preventing age-related cognitive decline, for example—would be a catastrophe.[14] Since it is most unlikely that anti-ageing

[14] This realisation is ancient: Tithonus was the son of the Trojan King Laomedon; he fell in love with Eos, the titan of the Dawn, who begged Zeus to make Tithonus immortal. Zeus agreed, but Eos had forgotten to ask that Tithonus should have the ageless immortality of the Gods, so he grew ever more decrepit but could not die:

research will succeed perfectly at the first attempt, it is practically certain that there will be a period of partial success and therefore also a risk of serious adverse outcomes. The indifference of anti-ageing advocates to this issue is, unethically reckless, by any standards.

The argument that the deaths of the very old are less deplorable than those of the young applies, however, to present day circumstances, since we have clearly not abolished ageing just yet, so that today's lives do not have equal potential duration and therefore are of unequal value. This is important because we are not just talking so much about the ethics of abolishing ageing, as about the ethics of anti-ageing research, where the likely duration of current lives is relevant because anti-ageing research has resource allocation implications which affect the likely duration of current lives. As de Grey (2005a) notes, it could be that resources spent on "vaccines for African children" would save more lives than resources spent on anti-ageing research. This issue bears most heavily on the priority anti-ageing research should occupy in relation to other research, but in this context should be pointed out the ethical principles implicit in de Grey's response: funding vaccines for African children rather than anti-ageing science would be a mistake, he argues, "given that a cure for ageing will confer a much greater increase in its beneficiaries' life expectancy than a cure for any disease can do in the absence of a cure for ageing (and that there will

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But when the first strands of grey hair started growing
from his beautiful head and his noble chin,
then the Lady Eos stopped coming to his bed.
But she nourished him, keeping him in her palace,
with grain and ambrosia. And she gave him beautiful clothes.
But when hateful old age was pressing hard on him, with all its might,
and he couldn't move his limbs, much less lift them up,
then in her heart she thought up this plan, a very good one indeed:
she put him in her chamber, and she closed the shining doors over him.
From there his voice pours out—it seems never to end—and he has no strength at all,
the kind he used to have in his limbs when they could still bend.

(Hymn to Aphrodite, *Homeric Hymns*, trans. by G. Nagy, www.courses.dce.harvard.edu/~clase116/txt_aphrodite.html, accessed 16 July 2007).

Tennyson wrote a version which differs in that Eos continues to love Tithonus despite his decline:

Me only cruel immortality
Consumes; I wither slowly in thine arms,
Here at the quiet limit of the world,
A white-hair'd shadow roaming like a dream
The ever-silent spaces of the East,
Far-folded mists, and gleaming halls of morn.
[…] Why should a man desire in any way
To vary from the kindly race of men,
Or pass beyond the goal of ordinance
Where all should pause …

also be far more beneficiaries) … [this is like] the comparison between shooting one person and bombing a skyscraper." The claim is simply that if people are going to die, it makes very little difference whether they die sooner or later—de Grey offers as support the ethical observation that it is not usually considered less wrong to kill someone by putting a bomb under their car so they die tomorrow than to shoot them today.

This is the 'indifference to inequity' that is mentioned above. The underlying but unstated claim is that an increase in life expectancy is so valuable that it overrides all other considerations, in particular the distribution of life expectancy (the inclusion in parentheses of the number of people who will benefit is revealing). The value to be given to an increase in life expectancy in relation to issues such as the distribution of life expectancy seems to be the fundamental ethical question about anti-ageing science—de Grey is right that if we answer this question as he does, agreement with his position follows, and if we answer it differently, disagreement on every point follows as well. No case has so far been made according to which an increase in life expectancy trumps all other values.

The practical issues that we would have to work through if life expectancy was markedly increased have given rise to much discussion. Would people work for the same proportion of their lives or the same number of years? Since neither the breadth nor duration of experience would vary much among workers, how would promotion and 'seniority' operate? Caplan (2005), among others, has answered these questions by agreeing that something would have to be done to deal with the workplace effects, but leaving the question of exactly what to a later stage. After all, he points out, we have successfully adapted society to a life expectancy of 75 or 80 instead of 35 or 40, so why not 150 or 200? This is a little disingenuous, first because the increase from 35 to 70 was due to a decrease of infant mortality and not to increased adult longevity, so it cannot be considered as a precedent for anti-ageing science, second because an increase in life expectancy at age 20 from 60 to 200 years is a much greater change than any we have so far seen, and third because the track record of painless social adjustment to new and rapid change is, overall, poor. Another inevitable consequence of a marked increased life span, and a *prima facie* seriously negative outcome would be overpopulation. De Grey has pointed out that since he does not propose emigration to other galaxies (he is a scientist after all), there is only one way to avoid overpopulation. Fortunately it is simple: no more children (De Grey, 2004).

The most important, because the most radical, challenge to the anti-ageing project is a question Daniel Callahan has asked repeatedly, without getting a sensible answer: Why on earth (as one might say) would we want to live longer? (Callahan, 2000, 2003) After all, a cure for ageing will make life longer but not necessarily better, because it is not the duration of life that makes it good or bad but what happens in it. There is simply no reason at all to suppose that people who now have unrewarding careers and unhappy families would have rewarding careers and happy families if they lived longer.

The question can be put more crudely: although we have a sense that ageing is the enemy, on looking closer at the situation, we see that everything we value in life is dependent on ageing. What sense is there in a family life where parents, grandparents and great-grandparents are all exactly the same as their children, grandchildren and great-grandchildren (let alone when we have dealt with over-population by not having children), or of love without loss? What sense is there to a career or to politics where heads-of-department and Presidents are immortal? How exciting will any tennis tournament be when an ageless Roger Federer wins for the 1,000th consecutive time? To put this in another way, indefinite life is inhuman because everything human in life includes finitude and transition. So the Buddha said: "Where there is nothing, where naught is grasped, there is the Isle of No-Beyond. Nirvana I call it—the utter extinction of ageing and dying."

The response of de Grey and others in their published papers is that nothing—neither children, nor equity nor Rafael Nadal's chance of ever winning systematically all tennis competitions is as important as the opportunity for people to live indefinitely, whatever that life is to be: "the ghastliness of ageing … [is] worse than anything that curing ageing might cause." Curing ageing will create challenges, but they will probably find solutions—and if they do not, is there a requirement that a good life should confront no challenges?

The usual case against anti-ageing science is that it is wrong: the problems of life in a world of ageless people either cannot be solved or can only be solved at the cost of making life uninteresting. The "EMBO Report" Special Issue and several authors make this case, and even those who disagree assume that the battle over the ethics of anti-ageing science is to be decided by arguments over the desirability or otherwise of life in a world of ageless people. Equity issues are secondary, since, although the likely cost of a cure for ageing will mean that

not everyone has access to it, a cure for ageing is, in this respect, no different to safe drinking water.

The flaw in this case against anti-ageing science is not that it is wrong—as it may be possible to solve the problems of life in a world of ageless people—but that it is irrelevant. The advocates of anti-ageing science need not be troubled by any of the ethical or practical objections to a world *of* ageless people, because none of them apply to a world *with* ageless people. The cure for ageing will be restricted to a very small number of people—very small indeed, because the fewer the ageless the greater their advantages and the fewer their problems. The more convincing one finds the arguments that the problems of life in a world where everyone was ageless would be insurmountable the more certain one should be that the solution will be restricted access to the cure for ageing. Alex Mauron is quite right that "evolution needs mortality",(Mauron, 2005) but it does not need mine—his and yours will do perfectly well. A "career" and "Wimbledon" make no sense when everyone is ageless, but as much sense as they do now if ageless people are rare. Callahan is right that a long life can be unhappy, but people with unsuccessful careers will not be among the ageless. If the ageless are sufficiently few we can have as many children as we like. The cost problem with a cure for ageing is not that too few people will be able to afford it, but that, whatever it costs, too many people will be able to afford it. It is superfluous to ask whether the methods by which the ageless are selected will be ethically defensible: this project is indifferent to inequity in the grandest possible manner.

a. What Should We Do About Anti-Ageing Research?

It has been pointed out that ethicists are distressingly prone to make themselves into arbiters of ethical dilemmas, in defiance of the right they otherwise claim for ordinary people to choose for themselves (Luck and Hall, 2005). This is especially important in relation to anti-ageing research, because the scale of consumption of purported anti-ageing preparations suggests that a real anti-ageing treatment would be enthusiastically embraced, whether ethicists thought it was a good idea or not. Since it has been impossible to prevent any feasible scientific research when many ordinary people agree with ethicists that it is a bad idea, so the possibility of preventing the development of a cure for ageing would be most unlikely, on condition that it was scientifically possible and that only ethicists condemned it.

Banning anti-ageing research is likely to be ineffective and undesirable for yet another reason: the processes involved in ageing are, as we understand it at present, so fundamental that banning anti-ageing research means banning all basic biology.

If anti-ageing research is not to be prohibited, two questions need answers: how should we react when public support is sought for a programme of anti-ageing research, and how should we react when an experiment or trial on anti-ageing is proposed?

A warning has been expressed against the whittling away of ethical and technical standards by a culture of exceptionalism in anti-ageing research as also against a culture of bad-exceptionalism, i.e. the idea that exceptionally high or rigid standards should apply to anti-ageing research. It seems to me that this would be ethically inappropriate, but in any case unnecessary. The principle that arises concerning experiments and trials aimed at anti-ageing is the universally accepted principle that research must not go ahead unless it is ethical, and that research is not ethical unless the risks of the research are proportionate to the reasonably anticipated benefits. All of this research will occur in the phase of failure (even the culminating successful trial, if there is one, will be planned and initiated in the phase of failure), and the risks of the phase of failure will be high and the potential benefits at each step relatively slim. To account adequately for risks, it will be necessary to widen the event horizon beyond the rather narrow one used now in order to include the risks to public finance of creating a 'global nursing home', for example. Nevertheless, the event horizon at which risks and benefits are judged should be that of each individual experiment or trial. Whether eventual success is to be considered a risk or a benefit is for ordinary people to decide—a choice which could be encouraged for ethical reasons but which they are entitled to make for whatever reasons they deem adequate; yet these considerations on the ethics of success should not be given weight in the ethics of the phase of failure.

The priority that anti-ageing research should have for public support should also be determined in relation to a relatively short event horizon. As public resources are an issue, the claim of equity is very strong: and the equity that is relevant is that of the present, because the future cannot be held to have an equity interest in the discoveries we might or might not make on their behalf (Jonas, 1969). In particular, the argument that anti-ageing research should not have priority on public resources until people everywhere have a fair chance of living long

enough to benefit from it, seems to me to be a valid argument, and acting on it would be consistent with equitable resource distribution. (Brinsmead and Williams, 2004; Daniels and Sabin, 2002; Seabright, 1993).

7.3.5. Conclusion on the Debate: Ethical or Cultural?

As Stephen Hall makes clear in his book "Merchants of Immortality": Chasing the dream of Human Life Extension (Hall, 2003), scientists and entrepreneurs will persist in their efforts to combat ageing as well as disease, with or without government funding, and with or without the approval of bioethicists, philosophers, and other critics. So what can we do?

Stephen Post (2004) proposed to establish an "appropriate ethical framework" that takes into account in a balanced manner the 3 perspectives of i) natural law, ii) equalitarian justice, and iii) beneficence. Although the conclusion he reaches is that the goals pursued for prolongevity and a society of longer life is ethically valid as a potential means to the beneficent improvements of the many age-susceptible diseases, he recognises that "we do not have much choice but to move forward. The goal of prolongevity, as preventive of morbidity is rooted in the reality of the 80-year-old who has struggled with hip replacement, a diagnosis of dementia, retinopathy and related depression. It is common sense no one wants that for his or her old age if there is a healthy alternative." (Post, 2004) But on the other hand, he also wisely states that "we simply cannot predict the future, […] but there is reason to urge caution, the technology to slow the ageing process may be coming nearer to reality yet the goal of prolongevity has not been carefully considered. In a time when biotechnology is allowing for the reconstruction of both nature and human nature, all thoughtful citizens must ponder the implications of potentially dramatic change, […] enhancing the human condition could in fact diminish human dignity (cloning, genetic testing, human enhancement, bioengineered bodies and minds, etc.)."

Biogerontologists, gerontologists, and geriatricians as well as society at large would benefit from anticipating some of the consequences of AAM and deliberating on specific issues that concern the protection of the freedom and safety of the population and individuals. For example, if dramatic increases in healthy life expectancy and life span become feasible through those new interventions, to whom should these be allocated in society? One could also argue that, if the values that steer science and society lie into reaching a decent quality of life for as many people and for as long as possible, AAM interventions

and even human enhancement could be viewed as increasing the chances of a decent life, remotivating older men and women as they can regain an attractive body shape, and boost the brain performance, hence potentially decreasing the alarming suicide and depression rates in late life all around the world (WHO, 1999).

Serious ethical issues would be raised if the life-saving or chronically protecting interventions were not universally available, but allocated in accordance with wealth, social, and political status, ascribed 'merit', or some other distinguishing criteria. Here again, it could be argued that the gap between rich and poor in access to technological goods has always existed (e.g. buying the first very costly computers, cells phones, etc.). As progress evolves, we witness a 'democratisation of low-cost technologies' and a 'commercialisation of low-cost medicine': is this positive or are there counter-indications for the quality of life of the individual? As long as health hazards and safety are protected: why not?

Alternatively, if access to effective anti-ageing interventions were unlimited, what we now term the 'ageing society' would become transformed into the 'long-lived society', as a new large stratum of the prolonged old would be added on to the older age groups that are currently described by a trio of conventional labels: the young-old, ages 65–74; the old-old, ages 75–84; and the oldest-old, ages 85 and older (Suzman et al., 1996). A long-lived society populated by numerous prolonged old people with enhanced functions would certainly witness radical changes in the nature of family life; labour, housing, and consumer markets; politics, public policies, and the law; and virtually every social institution. Pushing speculation a step further, one could even imagine the raise of a new 'human ageing species'.

Such potential consequences of effective anti-ageing interventions have much more profound and far-reaching implications than other current biomedical policy issues such as the ethics of human cloning, as it concerns everyone and all ages, and not only older people, but future generations as well. If science succeeds in decelerating or arresting ageing, the consequent transformations in the nature of individual and collective life may well be drastic. The hierarchy of age might disappear and the very nature of time as a growing and developmental factor would be questioned; who becomes wise if not with time and age? Where is the value of wisdom and life experience if not through age and the marks of time?

Despite its importance, such societal and medical mutations have rarely been addressed to date, and certainly not in forums that reach a wide public and also policymakers. More active leadership by scientists is required to bring together biogerontologists, medical researchers and practitioners, behavioural and social sciences, ethicists and the humanities in order to help the public understand the goals and potential consequences of anti-ageing and prolongevity research and deliberately consider its implications. Anticipating and reflecting through open discussions on the shape of such innovations and their impact, may wisely open the way to shaping the future of the anti-ageing science and its social consequences.

Juengst et al. (2003a) argue that scientists have a responsibility to inform the public and present 'the real story' about anti-ageing interventions. An example exists in U.S., where two members of the Gerontological Society of America—biologist Tom Johnson and political scientist Robert Binstock—have formed an Interest Group on the Societal Implications of Anti-Ageing Research[15] that met for the first time at the 2003 Gerontological Society of America annual scientific meeting, and will continue to meet in the future. In 2005, Tom Johnson underlined that an increasingly large fraction of the discussion has focused on the feasibility of life extension for humans. A majority, but not all, of the participants who have attended these meetings seem to share the view that radical extension of human longevity will become possible and could make good sense. He even stated further that "there is no question that within the last quarter century, based upon the ground-breaking research of dozens of scientists, the field of biogerontology has undergone a Kuhnian revolution; and it is certainly true that modern research focusing on life extension (albeit almost entirely in animal models) is now hot."

Such initiatives are a first but a small step to clarify the scientific and ethical dimension as well as the societal implications of AAM; such initiatives should be replicated and harnessed on a larger scale and not only among ageing specialists, but with technocrats and with those most concerned, the general public. But the question remains as to how effective such public education campaigns will be if the temptation for many journalists to sensationalise minor scientific discoveries seems irresistible.

[15] http://www.geron.org/interest.htm

Fundamental questions remain unanswered as to the limits between research progress, ethical clinical practice and patient's rights to choose an anti-ageing lifestyle with the large array of interventions and products available. The question of how and to what extent governments and society are responsible to protect consumers and patients remains at the core of the debate. From risk assessment to safety and quality control, all medical and non-medical anti-ageing products, treatments and care will have be the subject of ethical debate for as long as appropriate and clear regulations and legislation will not be in place, which is the objective of the recommendations in the next chapter.

8. Synthesis

Anti-ageing medicine (AAM) is a complex scientific field bringing together more and more disciplines who wish to harness the latest technological progress in different fields of medicine. Applications range from the nano, micro-level to the application of external engineered biomaterial or robotics to the human body. Pulling together technical and medical scientific findings, from the laboratory to clinical practice onto public health, is no longer in the sole hands of the medical establishment but is also in the hands of the private sector, with the emergence of medical start-ups or flourishing health businesses. AAM can embrace many specialised fields in a joint venture: from biomolecular regeneration processes to engineered solutions with chips and bioregulator devices monitored with wireless systems, from surgical procedures with the latest generation of robotic or laser devices to bioengineered implants. Scientific progress often brings both benefits and risks in the same package, therefore progress cannot be halted unless there is serious danger for the individual or society which brings the ethical issue at the centre and calls for legislation. This report reflects this precise dilemma: If on one hand, the scientific review of AAM demonstrates the importance of considering different levels of evidence and absence of evidence linked partly to an ongoing scientific and technological progress, on the other hand, the survey undertaken within the framework of this TA-SWISS study among ageing experts, practitioners and specialists show very diversified opinions on AAM.

8.1. Expert Survey: Diversity of Opinion on AAM

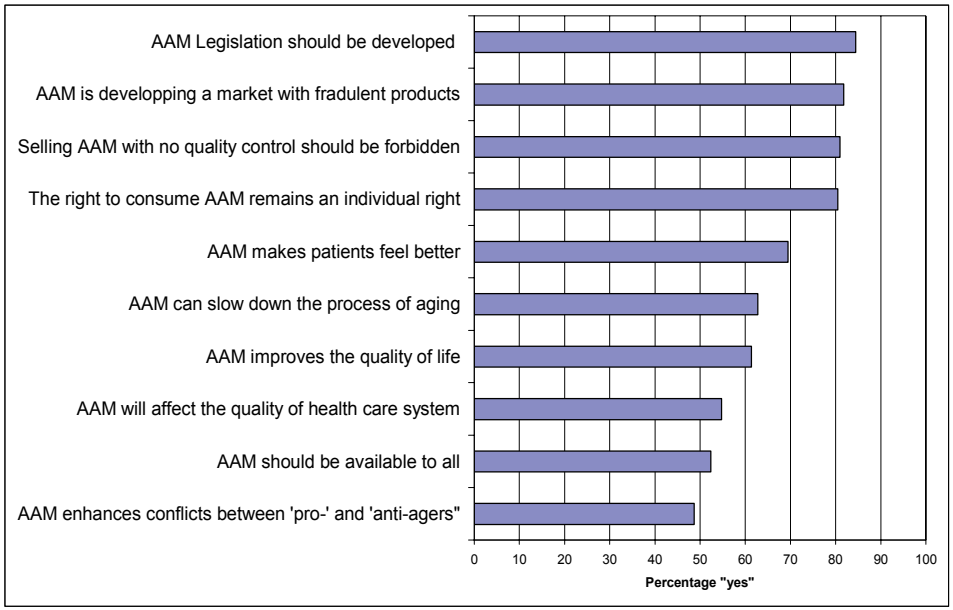
Contrary to what is observed regarding the 'better ageing' approach which is today recognised as based on solid evidence, little is known on the recognition given by international experts on AAM. The opinion survey conducted over a year with experts from different disciplines linked to ageing shows clearly that there is no consensus among experts on AAM, what AAM is, what works, what the risks and benefits of AAM are, nor on the importance of ethical issues.

8.1.1. No Clear Consensus on AAM

This point is illustrated in figure 7a and 7b. To questions such as "Does AAM bring a higher life expectancy?", "Will AAM reduce the age-related prevalence

of illnesses?", "Should AAM be available to all?" etc., the general trend is that about half of the interviewees responded "yes" and the other half "no".

Figure 7a: Expert Survey Question on AAM Impact: "What is the future of AAM?"



8.1.2. Distinct Positions About AAM Are Found According to the Disciplines

Geriatricians: The survey shows also that the majority of geriatricians condemns AAM and is resistant to any AAM interventions, while most of them apply and recognise 'better ageing' interventions. They also underline ethical problems, in particular the fraudulent way science is used and abused to promote AAM combating the signs of ageing and the aggressive marketing with misleading information to consumers.

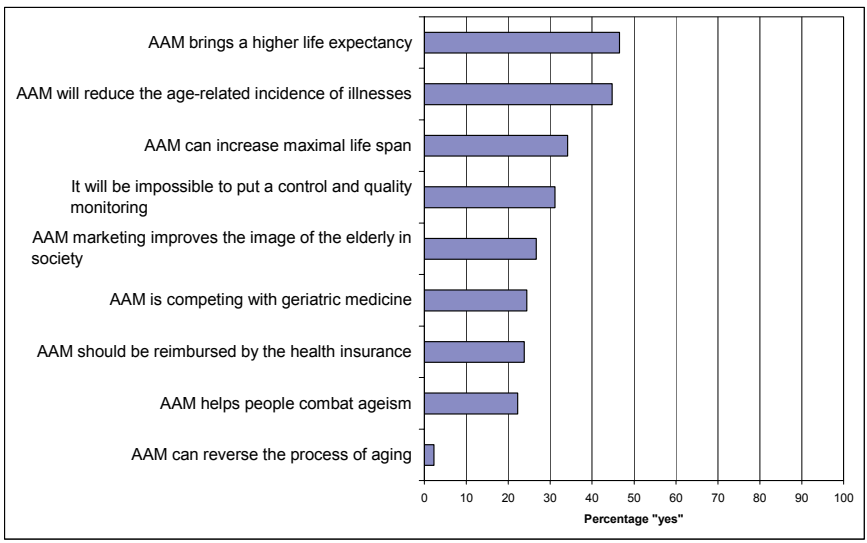
Researchers in fundamental science, such as biogerontologists, are keen on the research and development of new interventions and do not see a problem in the aims of AAM per se, nor do they foresee any ethical problems in AAM

research. Nevertheless, they do underline the importance of controlling and regulating the products marketed to avoid fraud and risks for the population.

Medical practitioners from different disciplines are cautious but not opposed to AAM, they see efficient applications of different interventions on a case-by-case basis and use them in their practice, but they also insist on the patients' free choice of those interventions.

In Japan, the situation is quite different; as there are rigid state regulations on the products sold, far fewer conflicts arise from the concept of AAM. Although the development of the AAM movement in Japan is quite recent, it is very fast growing and does correspond to the fascination of Japanese culture for high-tech and robotics (see 5.6.2.b and 7.2.3.). After a few years of confusion a clear separation exists today between two movements which have different congresses and journals: the medical/scientific AAM community and the AAM business and technology interest groups.

Figure 7b: Expert Survey Question on AAM Impact: "Will AAM affect the following factors?"



AAM brings together a vast array of professions and sectors interacting or counteracting with each other: These professions include biomolecular and biotechnology specialists, medical doctors, health professionals, aestheticians, engineers, manufacturers, environmentalists, etc. Within the medical field different specialities, which a few years ago were not concerned with ageing, today include AAM protagonists (e.g. endocrinologists, gynaecologists, dermatologists, ophthalmologists, orthopaedists, surgeons, dentists, etc.).

The paradox between geriatricians and AAM specialists is the pace of recognition they are living: while, after decades of existence, geriatric medicine is still struggling to get acknowledged worldwide as a medical specialty with a specific curriculum, AAM is fast developing and used by other medical specialities. Thus, at least in Europe, AAM is perceived as a non-specialised field eroding the recognition and solid establishment of geriatric medicine.

This scientific review and expert opinion survey show blatant gaps of information on the AAM market, and the position of consumers of all ages on AAM.

It is therefore obvious that more clarity is required through further general and specific studies as well as data collection and reporting mechanisms in Switzerland and elsewhere as stated in the recommendations. Furthermore, given the extraordinary rapidity of high-tech biotechnology in the medical field, it will be increasingly crucial to guarantee continuous education in the field of high-tech medical progresses and biotechnology if a country wants to provide top quality in research and medical application.

This report has gathered various elements to differentiate between ‘Better Ageing’ and ‘Anti-Ageing’, not forgetting that there is an area where both ‘better ageing’ and ‘anti-ageing’ interventions overlap.

Contrast between better ageing and anti-ageing can be outlined as follows (table 12):

Table 12: Contrast between Better Ageing and Anti-Ageing Medicine[1]

	Better Ageing	Anti-Ageing
Funding of concept	1950–60s: successful ageing 1990s: active ageing	1990s: research & development 2000: high-tech AAM
Root of the movement	Based on traditional geriatric medicine, social scientists react to 'declining model' and claim plasticity and gain in ageing	Progressist movement started by Dr Klatz and Dr Goldman in the U.S. and spreading worldwide. Reaction to the geriatric tradition with mere focus on early detection and interventions claiming control of ageing process and upper performance limits
Concerned population	Population 50+	Selected population of all age groups
Attitude	Accepts the ageing process as natural but optimising active and healthy lifestyle choices	Does not accept natural ageing but combats ageing signs and symptoms Refusal of following normative ageing but setting a normative anti-ageing attitude of seeking young looks and peak performance at any age
Objectives	Prevention, care and cure of age-related pathologies and disabilities	Prevention, energy boosting, enhancement of all body functions, and appearance medicine
Primary research & development (R&D)	Geriatric medicine: - Understanding disease, functionality, treatment and rehabilitation in the ageing process (from young old to the oldest old) - Includes centenarians and death issues Multidimensional geriatric assessment	Biogerontology: - Understanding the process leading to the failure of the system to restore and regenerate with new technologies - Identifying metabolic decline and compensation needed to counter age-effects - Taboo: death and end-of-life care Finding reliable biomarkers
Knowledge-based	Based on solid evidence and a long experience of scientific and practical knowledge	Based on different levels of evidence (from proven to unproven, with animals or humans) Rapid commercialisation of newest findings in diverse specialties and high-tech R&D business

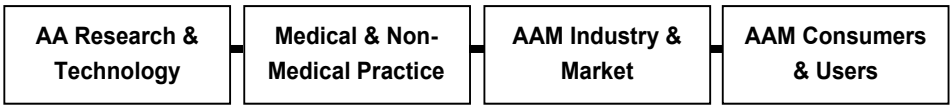
[1] This table is an indicator of the current general tendencies and views gathered from the interviews of experts as well as from the analysis of the material collected. Some points can be discussed depending what world view you take or discipline you come from. This table is intended for further discussion, debate and clarification in a constantly evolving field.

Preventive measures	Based on the traditional model (A) and better ageing model (B): - Daily life prevention and lifestyle measures - Routine screening and check-ups	Based on new medical findings, bio-technological promises, but also on hypothetical human-animal model: - Aggressive prevention/intervention - Continuous alertness on body changes - Early detection and biomarkers
Evolution of R&D medicine	Predictable: Public Health	Unpredictable: no control of private practice, free-market logic*
Evolution of consumers	Predictable—stable	Most likely a 'boom' touching all ages
Evolution of private sector	Predictable	Increasing/'boom'
Consumer: Level of risk	Low	From low to very high e.g. obsessive behaviour, averse health outcome (short- or long-term), financial deprivation with fake products
Consumer: Level of informed choice	Yes	No Risk of false/absent information – unknown components in the product
Risk for Society	Known	Unknown – multi-track agers: agers, better agers, transhumans. Pro-AAM vs. Anti-AAM: Total change of image of Ageing
Product counterfeit	Low risk	High risk*
Safety issue	Controlled low risk	From no risk to potential risk (internet, tourism, etc.) on to high risk (e.g. laser)
Labelling and marketing– information	Clear information and labels Low misinformation	Missing or misleading information and labelling
Legislation and regulation	Covering most interventions/products	Many products/interventions not yet legalised Commercialisation of medicine Confusion between medical treatment and food/goods (e.g. 'alicament', cosmeceuticals, nutraceuticals) Out-of-the-border legislation with globalisation-ICT effect*

Market covered	Daily living goods (sport, nutrition, etc.) Medical screenings for specific health conditions	From daily products to wellness to sophisticated products/interventions Sold through diverse channels (national/international)
Financing/payment	Public health – insurance	private/out-of-the-pocket
Financing: Affordability	Minimum guaranteed	From low cost to high cost
Market Evolution	Slow	Fast – growing access for all Low-cost to high-cost boom
Market Characteristics	Partnership between public institutions	private-public-partnership (PPP) consortium, or totally private
Medical curriculum in Switzerland	Geriatric medicine has been recognised as FMH specialty only since 1.1.2000. Compared to Europe, late recognition of continuous medical education.[2]	No official recognition of AAM as a medical specialty in Europe. The A4M certificates delivered for continuous education is not, at the moment, recognised by official Medical organisations in the world

In conclusion, the only central problem posed by classic prevention measures promoting 'better ageing' is that prevention policies and research are so far insufficient in Switzerland (e.g. Gutzwiller motion on prevention). For AAM, the situation is more complex (figure 8): While research and development, based on ethical standards, should be further encouraged, the transfer of medical technologies to clinical practice presents the same problems as in most other applied research areas. The most crucial issues lie in the transfer of scientific findings and the sharing of clinical successes with the market, consumers of all ages whatever their health conditions.

Figure 8: Process of AAM Research and Development Transfer



AAM health products and interventions can represent varied and potential physical harm and economic deprivation to the consumer, and especially to seniors. Scientific evidence shows that a variety of dietary and specialty supplements can have serious health consequences, in particular for the most

[2] http://www.sgg-ssg.ch/cms/media/pdf/SFGG/Profil%20Geriatrie%20Schweiz%20Internet.pdf

vulnerable groups of the ageing population. The boundaries between medical substances and commercial goods are being transgressed by new technologies, compounds, and micro-nutrients (e.g. nanotechnologies). What was formerly only in the hands of doctors and specialists is now made available to industry and even directly to the consumer and, what is still more serious, to seniors with underlying diseases or health conditions for which they are taking medication. Studies have shown that products sometimes contain harmful contaminants or larger amounts of an active ingredient than is indicated on the label. In the same way AAM interventions with high-tech devices such as lasers and flash lamps, have been reported to cause harm through promises of unrealistic results in private aesthetic or wellness centres. Therefore, considerable potential harm is at stake through misleading advertising and questionable health products and business practices.

9. Recommendations

Recommendations can be made in different areas of AAM of the development and production chain: biotechnological research and development, clinical trials, medical and non-medical practice, as well as AAM market and consumers.

9.1. Consumer's Safety and Information

Recommendation 1: High-Risk AAM Manufactured Products/Devices

Issue: AAM products on the market are considered to be dietary supplements or cosmetic products that are largely self-regulated. Unlike new prescription and over-the-counter drugs, these products are not covered by most of the controlled medical efficacy and safety tests. Some companies, which market products as "anti-ageing", either simply prey on the fears of the elderly or the ageing diseases, and/or make claims of miraculous effects of a given product (e.g. increasing energy, slowing down the ageing process, rejuvenating, building muscles or losing weight). Those claims often distort and misinterpret scientific findings (e.g. extrapolation of successful clinical cases or animal/laboratory research to the general population, distortion of findings, false data, or incomplete information). Some companies also portray a famous star in the show business or in medical science to support false claims. The marketing tactics of some of these companies as well as the products they promote, are often very sophisticated and difficult to control as shown by the U.S. case of the "Braswell Companies"; issues that need serious examination include direct personal mail marketing to consumer, sold directly to the consumer without going through retail outlets, as well as false claims and information provided (non existent scientific journal or medical doctor, text masquerading science), multinational business with different headquarters addresses with mail boxes outside the country and no name to make it difficult or impossible to identify for legal proceedings, etc. (U.S. Special Senate Committee on Ageing Hearing on Anti-Ageing Products for Seniors, 2001). It is important to underline that the refutations or endorsements of AAM on the basis of scientific evidence are often insufficient to discourage AAM users from purchasing the products in Switzerland and abroad (through internet or medical/wellness tourism).

Consequences: Companies who market misleading, risky, and/or ineffective products with the aim of convincing the consumer to purchase AAM products should give rise to serious concern. This situation can lead the consumer to the following situations:

a) *deception* by encouraging the purchase of a miracle product with either no efficacy or, at worst, adverse health effects (either due to unknown toxic compounds in the product, or no information on high risk exposure related to dose-dependent consequences, to health conditions, to age or sex);

b) *psychological abuse* through pressure and by instilling fear indicating that without a given product he/she will suffer in the future from all the ailments of ageing;

c) *financial abuse* of people with little money spending on and consuming false products;

d) *medical abuse* when promises to cure are made, which entails the risk of not consulting health professionals, thus worsening the consumer's condition.

Solutions: Measures must be taken promptly by concerned Swiss agencies, such as SwissMedic or the Swiss Federal Office of Public Health (SFOPH),[1] in accordance with the compulsory health insurance regulations (OKP).[2]

- *Legislation and existing control mechanisms should be enforced* to determine the safety of products specifically related to AAM in the context of differential population effects (healthy vs. non-healthy, adult vs. elderly vs. frail elderly, women vs. men). Agencies in charge of monitoring these types of companies should set a high priority on AAM preventive interventions and consider the creation of a public and professional first front office for fraud to respond promptly to the problems listed above as well as fraudulent cases triggered by the growing industry of dietary and specialty supplement, marketed through modern means of communication such as internet, international cable TV, direct phone, or mail marketing strategies.

[1] Swiss Federal Office of Public Health – www.bag.admin.ch
[2] Obligatorische Krankenpflegeversicherung OKP – e.g. see www.kpt.ch

- *Control of specific substances* composing sold dietary supplements and cosmetics products in Switzerland, in particular, products that merge pharmacological components in daily routine consumer goods (e.g. nutraceuticals, cosmeceuticals).
- *Labelling requirements and label control of AAM products* should be stricter with clear information and indication of health hazards and populations at risk (e.g. pregnant women, frail elderly).
- *Reinforcement of the judicial system* to halt instantly the product to protect the consumer and charge the perpetrator of criminal fraud (nationally and internationally) through the available Swiss Federal Laws.[3] SwissMedic "Vigilance for Medical Device" information sheet on persons placing devices on the market is not enough to guarantee the protection of the consumer,[4] and more should be done to control the international and national market of AAM devices (sold to medical and non-medical practitioners, but also directly to the client).
- *Transnational regulation:* Due to the transnational expansion of AAM and the difficulty for Switzerland and any national government to regulate the anti-ageing industry, there is a need for innovative strategies that can cross digital borders and intervene in the global environment in which AAM has taken root and continues to develop rapidly.

[3] Such as for example:
- "acts of negligent homicide" (art. 117 – http://www.admin.ch/ch/d/sr/311_0/a117.html)
- "negligently causing serious harm" (art. 125 – http://www.admin.ch/ch/d/sr/311_0/a125.html)
- "harm caused by public goods putting in danger life or health" (art. 47ff Swiss Federal Food Act/Bundesgesetz über Lebensmittel und Gebrauchsgegenstände: Lebensmittelgesetz, LMG – http://www.admin.ch/ch/d/sr/817_0/a47.html; http://www.heko.ch/toxin)
- "harm caused through medical products and devices" (art. 86ff Federal Law on Medicinal Products and Medical Devices/Heilmittelgesetz, HMG – http://www.admin.ch/ch/d/sr/812_21/a86.html)

[4] As a result of the introduction of the Law on Therapeutic Products (HMG) and the revision of the Medical Devices Ordinance (Medizinprodukteverordnung, MepV) on 1.1.2002, there are several changes concerning the reporting of serious incidents. The Swiss therapeutic products legislation transposes the four European Directives on Medical Devices 90/385/EEC, 93/42/EEC, 98/79/EC and 2000/70/EC into Swiss legislation. *In vitro* diagnostic medical devices are now also subject to self controls (art. 14 MepV), and serious incidents involving *in vitro* diagnostic medical devices must be reported (art. 15 MepV). The procedure described in this fact sheet for reporting adverse incidents applies to all medical devices.
http://www.swissmedic.ch/md/pdf/hmg-vig3-e.pdf

Recommendation 2: Non-Medical Practice of AAM Interventions

Issue: Non-medical AAM interventions with pharmaceutical substances (e.g. Botox in aesthetic cabinet) or with high-risk technological devices for AAM rejuvenation (e.g. laser or flash lamps) offer very low safety guarantee to consumers. In a consumer-driven context with high demand of AAM interventions at the lowest possible cost, many consumer safety issues arise that require better control and information. A few examples include:

- *Botox*: The offer of Botox injections is growing (a high-risk product if misused) with no medical supervision and incomplete information to clients.
- *Aesthetic surgery outsourcing*: All-inclusive offers of vacation in exotic locations with a one-week stay and very low cost AAM interventions—e.g. face and eye lifting, Dental Tourism ("Dental Vacation: Travel and Treat Your Teeth"[5])—are being offered to Swiss residents with first consultation in Switzerland but little guarantee of service and information on quality. Some of these patients suffer physical, psychological, and financial consequences.
- *Laser and other devices in AAM medical and non-medical practice*: While dermatologists and medical practitioners usually engage in further education when using new technologies and take full responsibility for their professional practice, non-medical professionals also have access to these new AAM technological devices for their private business (e.g. AAM skin treatment and rejuvenation) with no requirement of professional training for using these potentially risky devices. Cases have been reported in Switzerland of misuse of laser therapy on patients with irreversible de-pigmentation, yet many remain unreported.

Consequences: New technologies targeting AAM interventions are developing at a fast pace and are being sold without thorough testing or information concerning their possible adverse consequences for the user or for the 'client'. New medical devices, especially new models marketed and sold internationally to medical and non-medical practitioners are mostly regulated between the

[5] e.g. see http://dent.info.md/dental-care/dental-tourism-dental-vacation-travel-and-treat-your-teeth

industrial company and the practice. Thus, lack of the required further education is obvious and puts the patient at risk.

Solutions:

- *Technological device testing*: Before legally allowing current and future AAM technological devices to be sold, those devices should not only be carefully tested to comply with safety regulations, but should also be enforced on the basis of more detailed information (for the user and the client) on the basis of the risks incurred by specific groups and factors. Strict requirements and further education certification should be put in place for any medical doctor or non-medical professional wanting to purchase certain AAM technological devices (e.g. laser).
- *Strong regulation enforcement and information systems* should be put in place concerning new medical and aesthetic technologies (as in SwissMedic information sheet mentioned above) sold by foreign and Swiss companies to medical and non-medical practitioners in Switzerland. A Swiss 'Technology/Device Safety Label' is needed to make rapid assessments of safe AAM technology vs. high-risk technology clear to professionals and consumers, and inform the public about unsafe products and technologies that have been withdrawn. Partnership between SwissMedic, SFOPH, professional medical associations and patient/consumer organisations is needed.
- *Swiss medical societies* (specialised and non-specialised) should be called upon to play a stronger role in informing and warning the Swiss population.

Considering both recommendations 1 and 2, it is time to devise innovative mechanisms, such as a "TA-Medical-Business Watch" to help regulate the connection between clinical AAM interventions and the world of markets and consumers. Such a new structure could also open the way to case reporting for medical practitioners and users.

9.2. Research, Knowledge Transfer, and 'Ethiceuticals'

Recommendation 3: Insufficient Scientific Data

Issue: The AAM review brought to light the lack of scientific knowledge and consensus in various areas; two of such priority areas are:

a) *AAM substances, products and interventions:* insufficient research and inconsistent findings about substances, products and interventions linked to AAM. Furthermore, weak knowledge in 'integrative scientific developments' affects the smooth transfer of knowledge to application (e.g. therapeutic options such as statins, or the industrial development of robots and robotic devices in Japan to help the frail elderly).

b) *AAM market and consumer data:* The AAM market industry is blooming all over the world which makes supplements or AAM interventions increasingly popular not only to seniors but to all age groups, with a tendency to start at an ever younger age. While there is no available data in Switzerland to evaluate the evolution of the dietary supplement market, the U.S. has estimated that $27 billion or more is spent on supplements, and that 60% of the consumers are older Americans.[6] This trend is thought to continue and even to increase as Baby Boomers are reaching retirement age and are known to seek out new and different ways of ageing to maintain and improve their health. These data and projections are very useful to asses the amplitude of the phenomenon and for 'reality policymaking' such as taking improved technological, public health, and economic decisions.

Consequences:
a) *From science to practice and application*: Too little knowledge and information on a highly marketed 'eternal youth' concept can mislead practitioners and clients giving them false hopes and encouraging overconsumption of fraudulent products. Such products also entail high risks of secondary effects,

[6] The U.S. is one of the rare countries with surveys who have shown that the use of complementary and alternative medicine increased an amazing 380% difference between 1990 and 1997.

not only on health, but also on the financial situation of customers for over-spending. It should be added that the non-integration and transfer of knowledge on efficient 'better ageing/AAM' measures, can delay direct benefits for the population of all ages as well as its use in hospitals or homes for the aged. For example, a new treatment evidenced to reconstruct the bone mass in cases of osteoporosis, which went through the scientific hurdles to prove its worth, might not be used in homes for the elderly or might remain unknown to private practice for many years. The same can be said of technological devices readily applicable (smart house, surveillance, remote controls, etc.) that can be introduced today in the homes of the elderly; many new technologies could improve the quality of life of the elderly.

b) *From economic assessment to decision-making and legislation of production and consumption*: Switzerland, as many other European countries, lacks data and surveys on the practice of AAM interventions on the one hand, and on AAM market (production/consumption) on the other. This applies also to new modes of consumption such as outsourcing, medical tourism and internet sales.

What also requires analysis is the use of AAM products, interventions and technologies and their interaction with the health insurances, as well as their effect on the health system costs.

Solutions:
a1) Any research institute or consortium should be encouraged to contribute to progressive AAM proposals and technological solutions for an ageing population and benefit from appropriate support. Research is particularly necessary in the *identification of biomarkers of ageing and preventive tools for early detection—while recognising gender specificity at all levels of research*.

Special care is imperative in *age- and gender-sensitive research methods of testing products and medicines* (on animals as on humans). Caution is required for

i.) *bioequivalence methods:* Often in biomedical research evidence is transferred despite the fact that older persons representativity is lacking;

ii.) *age and gender effect:* Generalisation of efficacy from one age group to another as well as from women to men. Research

methodology on ageing population requires a complex framework taking into account multi-epidemiological and multi-factorial approaches, considering carefully age, period and cohort effects.

The Swiss National Foundation, the Swiss Federal Institute of Technology and other consortiums such as SwissNex, should all contribute and devote part of their budget to address the issues raised in this report. A Swiss National Programme could be launched in this area.

a2) *Knowledge transfer and sharing is needed among disciplines and multi-stakeholders* (e.g. caregivers, health professionals, geriatricians and gerontologists in hospitals, in the Spitex[7] system, as well as in the homes for the elderly, but also specialists in the pharmaceutical industry, engineering institutes and ethicists) to promote new technologies for the elderly and innovative prevention measures for all.

Two practical recommendations: The State Secretariat for Education and Research[8] opened a "Technological Information Platform" (TIP), in which a subtheme was devoted to AAM with an accompanying 'AAM task force', which would

i.) regularly *review international top on substances, products, interventions and industrial devices* directly applicable to the elderly. *A public catalogue and a website* would be produced on a yearly basis which would inform all actors of the newest 'better ageing technologies'. A classification of AAM products and interventions is necessary for specialists and should be integrated in international documents and in the WHO;

ii.) *convene an annual conference* with available webcast facilities and the media to launch systematically an evidence-informed campaign on AAM in Switzerland in partnership with SFOPH. A network could ultimately guarantee adequate communication between partners.

[7] The Spitex Association of Switzerland (Spitex Verband Schweiz) is the umbrella organisation of Swiss non-profit Spitex organisations. It is supported by the 26 cantonal Spitex associations. These, in turn, are affiliated with around 700 local charitable Spitex organisations. – www.spitexch.ch

[8] www.bbw.admin.ch

b) Surveys on AAM market and consumer's choice are urgently needed in Switzerland. SECO,[9] university institutions specialised in health economics and consumer markets should be called upon to design and conduct socio-economic surveys on AAM market (source, spending, etc.), but also on the user profile of AAM (e.g. age group, sex, socio-economic status, health condition, residence, etc.); they should be supported in their efforts. A data-monitoring system linked to SFOPH, Obsan, Health Promotion, SECO, OFAS but also a professional association like FMH[10] would follow the evolution of the market of the many AAM products and interventions in order to transfer the data to the 'Technology Information Platform' (TIP).

Recommendation 4: Scientific and Ethical Guidelines on AAM Interventions

Issue: Ethical guidelines and standards for AAM are essential guarantees for supporting research and development aimed at improving the quality of life and well-being of the population. AAM research in biogerontology, genomics, stem cell therapy, nutraceuticals, human enhancement, robotic caregivers, etc. is promising and a cause of satisfaction for a nation's development, but can also hold the seed of a non-avowed political aim which could be a much more serious threat to humanity (e.g. Botox as a bioweapon, robots as dehumanisers, transhumans for military use, etc.)

Consequences: While scientific researchers, such as biogerontologist, hold responsibility for developments of AAM findings on animals at the micro-biological level (with currently strict ethical research protocols), the transfer from animals to humans does not always follow strict ethical guidelines, especially when it comes to private practice. Currently, in medical practice, physicians play the role of self-regulators of AAM interventions applied according to each patient. What is needed is better evidence: prior to application and beyond randomised clinical trials, HRT interventions have shown the importance of testing on the diversity of population realities (sub-groups, age, gender, etc.).

[9] SECO State Secretariat for Economic Affairs – www.seco.admin.ch
[10] FMH – Foederatio Medicorum Helveticorum (Swiss Medical Association)

Solutions:

- *Intersectoral ethical guidelines for research protocols* should be elaborated by researchers, medical practitioners, and industrial manufacturers. Those guidelines could make AAM clinical interventions in private practice possible and thus avoid "killing scientific advancement", as AAM protagonists have reported (Dr Klatz' interview). It is important that the Swiss Academy of Medical Sciences SAMS,[11] especially the Central Ethics Committee (CEC), take a strong lead in developing such guidelines in conformity with ethical guidelines issued by internationally recognised agencies such as the Council for International Organisations of Medical Sciences CIOMS[12] and the work of the WHO Ethical Review Committee.[13]
- *Monitoring:* On the reporting of scientific and clinical results should be required and centralised at *a coordinated and central databank*. This would ensure more efficient data and information management which could be of direct benefit to sound medical practice, medical specialised association, the industry and consumers.
- *Think tank: An ongoing reflection on how to address ethics in the future development of AAM* would benefit all actors, and could be organised jointly by the above mentioned partners, but would also be placed before the dilemma between science and religions in matters of life and death closely linked to AAM. A national journal or platform could be created for this purpose.

Recommendation 5: Double Standard Research & Development: The Danger of a Market-Driven Scientific Development

Issue: Involvement of the market economy in fundamental and medical research holds the risk of a double standard in scientific development, a high-quality scientific research areas vs. a biased 'business-oriented' scientific area primarily concerned with selling a pseudo-scientific product. The Braswell case in the U.S. demonstrated how science and scientists can be deceived and used

[11] http://www.samw.ch
[12] http://www.cioms.ch/frame_guidelines_nov_2002.htm
[13] http://www.who.int/rpc/research_ethics/en

for the sole purpose of 'the profit-oriented industry'.[14] Conflict of interest between the logic of the market economy (aimed at selling a product/intervention, increasing the number of consumers and financial returns). For example, accepting consultancies, honoraria, gifts or bribes from manufacturers of medical equipment and pharmaceutics can give rise to conflicts of interest regardless of the arrangements or qualifying terminology: Financial conflicts of interest create a competitive relationship between the physician's fiduciary obligations to the patient and his economic self-interest. The ideals of science for the betterment of mankind could become a crucial issue in the future of AAM research.

Consequences: Part of the academic world is at risk of compromising its quality standards faced with the demands of the industrial world in financing the research. Furthermore, studies show that companies acknowledge that their intent was to influence the practice of physicians (Blake and Early, 1995). More than in any other area, technologically-related medicine needs to preserve integrity, as well as the quality of care, by avoiding unstable situations with a risk of ethical compromise. Scientists and medical practitioners can risk of losing their objectivity, as demonstrated by past research and clinical trials sponsored by the pharmaceutical or tobacco industry.[15]

Solutions: Ethically-based and approved research protocols and guidelines are particularly important in the field of AAM and technological applications to

[14] The marketing campaign of AAM products produced by Braswell was referring to science and scientist's quotes. The reality was that the scientific journal with a peer review group was fake and the renowned scientists were abusively mentioned as supporters or quoted with made-up sentences for selling AAM products by mail. The U.S. Senate could never sue *Braswell Co.* as they had anticipated a no man's land of multiplicating addresses in different countries.

[15] Example of cases reported which underwent a trials: in the U.S.
a) an assistant professor in orthopaedic surgery was fined $10,000 for implanting expensive knee prostheses without telling the devices were made by a company that paid him a $175,000 annual consulting fee;
b) the case of a corporation paying 80 cardiologists $1,000 each to implant three of the company's new leads in their patients and fill out some forms, ostensibly to see how the $29,000 product worked (see Jones et al., 2006);
c) the case of Prof. Rylander at the Geneva University with tobacco industry paying studies to prove reduced tobacco-smoking damage The trial's conclusion states, "the Commission proposes that it shall be forbidden for the members of the University to solicit funding for their research activities or seek consultancies, either directly or indirectly, from the tobacco industry. This measure aims at protecting the integrity of its scientists."
French: http://www.unige.ch/rectorat/pdf/Rapport_Rylander.pdf
English Summary: http://senate.ucsf.edu/townhallmeeting/RylanderAffair.pdf

human care. Information sharing among researchers, policymakers, and practitioners on their experience in research standards involving industry, should be developed taking into account all that has already been done in Europe and internationally or by, for example, the WHO Research Ethical Review Committee. Beyond the ethical debate, clear business ethics as well as ethical guidelines for industry-sponsored research must be sought, such as in the case of *Nestlé* sponsoring the EPFL in Switzerland for developing Brain Food. An ethical task force could be envisaged including highly qualified scientists of great moral integrity, to monitor the process; it is urgent to do so for the follow up of any present or future cases.

9.3. Improving Prevention and the Health System in Switzerland

Recommendation 6: Need for Better Access and Prompt Application of New Technologies

Issue: Today scientific and technological findings move at a much faster pace than ever before. In the context of a highly competitive world in direct transfer application of scientific evidence, Switzerland can play a key role on in avoiding certain key obstacles, through the following:

i.) *'speeding up' technological transfer:* biogerontological findings for direct clinical or routine application;

ii.) *covering the most effective prevention measures:* efficient better ageing/AAM interventions and products are considered as prevention; thus not covered by the insurance, they remain inaccessible to many.

Consequences: Scientific findings with profound therapeutic benefits for the population are about to emerge in many areas, as evidenced by clinical cases. For example, cases of hematopoietic stem cell therapy (transplantation) for cardiac failure offer some very promising results in different parts of the world. If the selective unregulated aspects of AAM consumption will continue, with limited access to quality and increased anti-ageing medical tourism, it is bound to have negative consequences, in particular unsuccessful treatments and

surgery or short/long-term deleterious complications due to the cumulative interaction of all AAM products. We are still unable to establish a balance between benefits and adverse effects. While the rich population will use more AAM products, even sold at higher prices in supermarket (e.g. omega3 orange juice, cocktail of acid folic-vitamin B6 B12), the more modest population might be deprived or choose cheap low-quality AAM products and interventions instead of the healthy natural products and food that could be quite adequate for good health.

Solutions: "Safe access to health is quality access to health." In a global and internet-driven information society, Switzerland should 'brand' its renowned quality on to health information and reliable technological interventions and products. This could be done for example with a symbol of Swiss ISO quality.

Through rapid quality certification, knowledge can be applied without delay and bring about informed behaviour, while guaranteeing safe practice. It is also of benefit to increase the monitoring of population and preserving 'territorial health' by a minimum control on international markets. Thus, the recommendation is to create an office in charge of validating new Swiss technologies and promoting rapid technology transfer and industrial production of therapeutic interventions or technological devices to the older persons but also to the institutions and private practices (e.g. Statin, chap 5.5.5. or Lokomat device for rehabilitation, cf chap. 5.6.2.c).

Recommendation 7: Need for Multidimensional Prevention

Issue: Despite the fact that preventive messages are known in Switzerland, there are large deficits in preventive care. In addition, the health behaviour (e.g. nutrition, physical activity) of a large proportion of older people is suboptimal. Unfortunately, disability and nursing home admissions are often seen as inevitable consequences of old age or disease rather than potentially modifiable events. A further difficulty is that prevention programmes have to address the particular needs of multiple sub-groups of older persons (health and functional condition, age, sex, etc.).

Consequences: The neglect of health promotion and prevention in old age profoundly affects costs and quality of life. It has been estimated that even a modest improvement of risk factors would result in a decrease of health care

costs of more than CHF 2 billion per year. In addition, functional status decline is a major factor affecting quality of life in old age. Health promotion and prevention can reduce disability and delay nursing home admissions, and therefore is an important factor contributing to a better quality of life in old age.

Solutions: Efforts should be made to improve health promotion and prevention in all older persons. Programmes should not be limited to single factors, but address multiple potentially improvable risk factors or deficits in older women and men. To achieve this goal, all stakeholders (such as governmental agencies, health insurance industry, health and social care services, professional groups, schools and universities) must contribute to this effort. Even if only 1% of current long-term care costs (approximately CHF 65 million per year) would be invested in health promotion and prevention, effective programmes could be implemented and offered to all older persons in Switzerland. With such an investment, an effective multidimensional health-risk appraisal programme could be offered to all older persons. A combination of health-risk appraisal and gender-specific incentives for using preventive care and improving health behaviour would certainly improve health and thus reduce health and social costs in old age.

Important preventive screenings are necessary and should be added to the already existing preventive medicine measurements (e.g. homocysteine, sensory and loco-motor and metabolic check-ups, etc.). Health insurances would also benefit if they supported, together with their 50+year-old clients, small preventive and wellness strategies[16] or technologically automated rehabilitation. Small investment could well hold big effects in reducing the long-term health care cost.

[16] A few pioneer insurances have already implemented some measures (e.g. fitness clubs).

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Future Developments of the AAM Study

This TA-Swiss study presented in this book has contributed to the development of several projects. It initiated collaborations to create new AAM-integrated concepts of hospitals and clinics as well as reflections for improving legislation, prevention and intervention measures in public health policies.

Among current achievements to be mentioned, the study served as a basis of the project "Wade Institute for the Health Future of Africa" ("*Institut Wade pour la Santé Future en Afrique*") initiated by his Excellency Dr Abdoulaye Wade, President of the Republic of Senegal in Africa.

The study was also provided in a presentation for the Russian Federation and enhanced collaboration with Prof. Vladimir Khavinson, Director of the Institute of Bioregulation and Gerontology in Saint-Petersburg.

It is scheduled to be presented at international and national meetings for further development of sound legislation and measures to protect individuals from abuse of inefficient or unsafe AAM interventions, and moreso to avoid neglect in applying efficient AAM measures which improves quality of life at all ages.

12. List of Experts of the AAM Study

As announced in the Acknowledgment section (chapter 11), below are listed the persons and institutions who contributed to this report by participating in the expert survey, the face-to-face survey, the clinical visits and interviews or in different ways by their most enriching input in the report.

A – International Experts: Contributors to the Report

Prof. Gianfranco Domenighetti, Universita della Svizzera Italiana (comment on the AAM market and economic data)

Dr Okan Kulen, private dentist, Geneva, Switzerland (paper on "Vieillissement dentaire")

Dr Heidrun Mollenkopf, Senior Researcher at the German Centre for Research on Ageing at the University of Heidelberg, Germany (position paper "Anti-Aging Technology and Medicine from a Socio-Ecological Perspective")

Dr Kaweh Mansouri, Jules Gonin University Eye Hospital, Lausanne, Switzerland (paper on "Technological Progresses and AAM in Ophtalmology")

Prof. Alex Mauron, Head of the Bioethics Research Teaching Unit, Faculty of Medicine, University of Geneva, Switzerland

Dr Leslie G. Olson, WHO Research Ethics Committee member and WHO technical consultant, Fellow of the Royal Australasian College of Physicians (position paper "Ethical Aspects of Anti-Ageing Science – A Point of View")

Emeritus Prof. Dr Walter Seiler, Head of Acute Geriatric Department, University Hospital Basel, Switzerland, until August 2006 (comments on nutrition)

Dr Stephan Sigrist, Swiss Gottlieb Duttweiler Institut (GDI), Switzerland (comment on the AAM market and economic data)

Barbara So-Barazetti, Evaluation Consultant, Lausanne (paper on "Anti-Ageing Medicine in Switzerland")

Prof. Andreas E. Stuck, Department of Geriatrics, University of Bern, Spital Bern-Ziegler, Bern, Switzerland (contribution on multiple interventions for better ageing)

Dr theol. Markus Zimmermann-Acklin, Lehr- und Forschungsbeauftragter, Institut für Sozialethik, University of Lucerne, Switzerland (comment "Some Ethical Challenges of AAM: a Moderate View")

B – International Experts Interviewed

Prof. Emile-Etienne Baulieu, Professeur of Biochimistry at the Paris Faculty of Medicine, INSERM, Professor at College de France

Heather Bird-Tchenguiz, MBA, organisor of the 3rd Anti-Ageing Medicine Conference in London in September 2006, A4M founder in UK, Founder and President of HB Health—directs two AAM clinics, Director of "World Academy of Anti-Aging Medicine", Director of British Society of Anti-Ageing Medicine

Prof. Paul Clayton, Chairman of the Food Group at the Royal Society of Medicine of London, speaker on "Alzheimer's disease: pharmaco-nutritional strategies to maintain the ageing"

Dr Suryaparakash Dubey, Health director, Hay Barn Daylesford, health cabinet and store, London, UK

Dr John N. Hathcock, Vice President, Scientific and International Affairs, Council for Responsible Nutrition, Washington, DC, USA

Dr Axel Kahn, medical doctor, writer and philosopher, Director of the Cochin Institute and of the Alfred Jost Federative Research Institute, Paris, France

Rosy Graham, Parents representative of paraplegic children and advocate for stem cell research

Dr Ronald Klatz and Dr Robert Goldman: Founders of Anti-Aging Medicine (AAM) and of the Academy of the Academy of Anti-Aging Medicine (A4M) in the U.S.

Dr Marco Traub, Research Director GeneMaLK and coordinator of the Trans-European Stem Cell Therapy Consortium, Lugano, Switzerland

Dr Stefan Woerly, MD, PhD, specialist in stem cell biomaterial, Research Centre on Vegetal Macromolecules, National Scientific Research Centre, Grenoble, France

International Longevity Centers (ILC), in New York, USA:

Prof. Robert Butler, founder and director of ILC: www.ilcusa.org,
Affiliate of Mount Sinai School of Medicine and co-chair of the The Alliance for Health & the Future

Prof. Victor G. Rodwin, researcher New York University, U.S., consultant for ILC, author of books on ageing in the city

in Tokyo, Japan:

Dr Shigeo Morioka, president of ILC, former CEO for pharmaceutics: www.ilcjapan.org

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C – Expert Clinicians and Research Institutions in Tokyo, Japan

Eiji Hayashi, manager JMEC Co. LTD, Company for laser devices for dermatology and surgery, Tokyo: www.jmec.co.jp

Dr Motoharu Hojo, President Mita Clinic, Cell Bank Co. Ltd, Regenerative medicine clinic: www.rdcell.com

Dr Kazuhiro Ito, director, Ginza Oct Clinic, Tokyo: www.ginzaoct.com and www.goct.jp

Prof. Nobuyuki Shioya, AAM Clinic Ginza, Honorary Director of the Clinic, Prof. Emeritus Kitasato University, Diplomate of American board of surgery and plastic surgery:
www.aac-clinic.com, www.anti-ageing.jp, www.woundhealing-centre.jp, and
blog: http://blog.excite.co.jp/shioya-antiageing

Prof. Takuji Shirasawa, Head of Molecular Gerontology and of the Ageing Genome Biomarker Research Team, Tokyo Metropolitan Institute of Gerontology TMIG, Tokyo: http://www.tmig.or.jp/research/A10.html,
Manager of Japan Society for Biomedical Gerontology, Director of the Japanese Society of Anti-Ageing Medicine,
Visiting Professor, United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology,
Director of Anti-Ageing Science Inc., a venture company founded in 2003: http://www.antiaging-science.jp/english/index.html

Dr Katsuya Takasu President Takasu Clinics, Tokyo, Nagoya, Osaka/Umeda, Osaka and Yokohama: www.takasu.co.jp and http://katsuya.takasu.co.jp

Prof. Kazuo Tubota, Chair of Ophthalmology, Keio University School of Medicine, Tokyo: www.tusbota.ne.jp

Other international experts consulted:

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French part of Switzerland:

Dr Raphaël Gumener, directeur médical, Institut Raphael, Geneva

Tom Gyger, directeur administratif (2007), “Easy Look”, Clinique Rive Droite: www.easylook.ch

Dr Ulrich K. Kesselring, Centre de chirurgie plastique “age-less”, Lausanne: www.swissaesthetic.ch/langues/al/doktor-ulrich-k-kesselring.html and www.age-less.org

Frederic Kuehne, Neocutis, Lausanne (informant for industry)

Dr Michel Pfulg, Laclinic, Montreux-Territet (Emission TV): www.laclinic.ch

Prof. Jacques Proust, Centre de Prévention du Vieillissement, Clinique de Genolier VD: www.genolier.net

Dr Thierry Waelli (directeur médical) et Mme Yaël Bruigom (marketing), Clinique La Prairie, Clarens/Montreux: www.laprairie.ch

Biotonus Clinique Montreux: www.biotonus.ch (on documents)

German part of Switzerland:

Dr Fiorenzo Angehrn, Klinik Piano – Swiss Health & Life Xtension Institute, Biel/Bienne

Dr Roland Ballier, President of the Swiss Society for Anti-Aging-Medicine and Prevention (SSAAMP)

Prof. Dr Renzo del Brun, gynaecologist, Bern (founding member of SAABA)

Dr Sascha Dunst, Pallas Klinik – Artemedic, Olten

Prof. Dr Johannes Huber (Vienna), Vice President of the Swiss Austrian Association for Anti-Aging Medicine (SAABA)

Dr Martin Jenzer, Klinik Projeunesse, Praxis für Ästhetische Medizin, Hergiswil

Dr Christian Köhler, Plastic-, Hand- and Reconstructive Surgery, Burn Center, Anti Aging Therapy, University Hospital Zurich (member of SSAAMP)

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Dr Roland Voëlin, “gaaz – ganzheitliches anti-aging zentrum”, Basel

Baxamed Medical Center, Binningen : http://www.baxamed.com

E – International Expert Networks Consulted

European Region Association of Gerontology and Geriatrics (IAGG-ER)

European Research Area in Ageing (ERA-AGE)

European Geriatric Medical Society (EUGMS)

International Association of Geriatrics and Gerontology (IAGG)

International Francophone Association of Gerontology and Geriatrics (FAGG)

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Swiss Austrian Association for Anti-Aging Medicine (SAABA)

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- United Nations Programme on Ageing:
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- United Nations Economic Commission on Europe (UNECE):
  Andres Vikat, Director, Population Unit, United Nations, Geneva
- World Health Organization (WHO), Ageing and Life Course Programme
- Association of WHO former Staff (AOMS), WHO, Geneva:
  Roger Fontana (president)
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  Florence Denmark (chair), Helen Hamlin and Virgina Hazzard†
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- International Network on the Prevention of Elder Abuse (INPEA)
- Geneva International Network on Ageing (GINA)

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13. Concise Glossary

ACETYL-L-CARNITINE

A biochemical compound which declines with age. This compound facilitates the ability of mitochondria to produce biochemical energy in the form of ATP.

ACROMEGALY

A disorder marked by progressive enlargement of bones; usually caused by overproduction of growth hormone due to pituitary cancer.

ADAPTOGENS

Plant remedies which help the body to adapt to chronic stress.

ALZHEIMER'S DEMENTIA

An age-related form of brain damage resulting in severe forgetfulness, inability to look after oneself, cognition problems and disorientation.

ALZHEIMER'S DISEASE

An ageing-dependent disease characterized by loss of memory. Risk factors include both genetic and environmental factors. Age of onset varies from the late 40s for patients with early-onset genetic risk factors, to 65 and older for most other patients.

AMINOGUANIDINE

A compound used to reduce non-enzymatic glycosylation of proteins.

AMYOTROPHIC LATERAL SCLEROSIS

An age-related neurodegenerative disease caused by premature death of motor neurons; also known as Lou Gehrig's disease.

ANTIOXIDANT

A compound and/or enzyme that neutralises reactive oxygen species, thereby reducing oxidative stress. Substances which reduce or fight free radicals.

APOPTOSIS

The “falling of the cell”. It is a natural type of orderly and programmed cell death which eliminates damaged cells while leaving healthy cells behind untouched. It is the opposite of “necrosis” which is a disorderly and widespread cell death.

AUTOLOGOUS

Pertaining to a tissue or structure occurring naturally and derived from the same individual.

BIOMARKER (OF AGEING)

An age-related change which reflects the physiological age of an individual, in contrast to the individual’s chronological age.

CALORIC RESTRICTION

A diet strategy to limit the caloric intake, while supplying all other essential dietary ingredients. This extends life expectancy and delays the onset of age-related disease in rodents.

CATALASE

An antioxidant enzyme that destroys hydrogen peroxide, converting it to water and oxygen.

CENTENARIAN, SEMI-SUPERCENTENARIAN, SUPERCENTENARIAN

A person who has lived for at least 100 years is a centenarian, for at least 105, a semi-supercentenarian, and for at least 110 years, a supercentenarian.

CHELATORS

Compounds that tightly bind metal ions, thereby preventing their normal chemical activity.

DAF

A symbol for nematode mutants with developmental defects.

DEHYDROEPIANDROSTERONE (DHEA)

A circulating adrenal steroid hormone that has been widely promoted as an “anti-ageing” hormone. Circulating levels decrease with age.

DYSKERATOSIS CONGENITA

A congenital condition characterized by defects in highly proliferative tissues such as skin and bone marrow.

EMBRYONIC STEM CELL

A stem cell obtained from an embryo (see STEM CELL below). An embryonic stem cell is assumed to have the potential to differentiate into any kind of cell, and therefore to be the most versatile in cell replacement therapy.

ESTROGEN

The major female hormone, produced primarily in the ovaries.

FIBROBLAST

One of the major cell types found in human skin. Fibroblasts have been developed as a model system for studying cellular ageing.

GERMLINE

Cells destined to become either eggs or sperm cells.

GREEN FLUORESCENT PROTEIN (GFP)

A specific protein that fluoresces green. The gene for this protein is used as a "reporter" transgene because the presence of GFP is easy to detect in tissues.

GROWTH HORMONE

A hormone produced in the pituitary that is essential for normal growth. Circulating levels decrease with age, and growth hormone replacement has been promoted as a possible anti-ageing intervention.

GROWTH HORMONE RELEASING HORMONE

A hormone that directs the pituitary gland to produce growth hormone.

HORMONE

A substance produced in one tissue, but usually acting on another.

INSULIN-LIKE GROWTH FACTOR I (IGF-1)

A factor that resembles insulin and stimulates cell growth.

LIFE EXPECTANCY

The average length of life of a population of individuals.

LIFE SPAN

The maximum life span defines the age of death of the longest-lived member of a population.

LYMPHOCYTES

White blood cells involved in producing an immune response.

MELATONIN

A hormone produced in the pineal gland, which has a role in the sleep/wake cycle. Melatonin supplementation has been promoted as a possible anti-ageing intervention.

MORBIDITY

The relative incidence of disease.

MORTALITY

The relative incidence of death.

MYOCARDIUM

Heart tissue.

NEMATODE

A small worm, usually soil-dwelling, which has been developed for biomedical research because of its well-characterized developmental programme. It is a useful model system for studying ageing because of its short life expectancy.

NUCLEAR TRANSFER

The transfer of a nucleus from one cell into another cell lacking a nucleus.

OSTEOPOROSIS

A condition characterized by decreasing bone density with age, thus increasing the risk of bone fracture.

OXIDATIVE STRESS

The process whereby cellular macromolecules are damaged by reactive oxygen species, produced mainly in the mitochondria, leading to dysfunction.

PARKINSON'S DISEASE

An age-related neurodegenerative disease caused by premature death of neurons in the substantia nigra; characterized by rhythmic muscular tremors.

PITUITARY

A gland in the brain that produces several hormones, including growth hormone.

POST-MITOTIC TISSUE

Tissues in which few, if any, cells are capable of replicating, such as tissues in the brain.

REPLICATIVE SENESCENCE

A condition characterized by the loss of proliferative capacity in individual cells. Telomere shortening is one cause of this.

RETINAL PIGMENT EPITHELIAL CELLS

Pigmented cells found in the retina. These cells are essential for vision.

RETINOIC ACID

A compound that stimulates cells to differentiate into specific cell types.

STEM CELL

A special kind of cell that divides asymmetrically, in the sense that it appears to have the ability to continue to produce daughter cells without undergoing replicative senescence.

SUPEROXIDE DISMUTASE (SOD)

An antioxidant enzyme that converts the superoxide anion to hydrogen peroxide.

TELOMERASE

An enzyme that synthesises telomeric DNA (see TELOMERE below).

TELOMERE

The non-coding DNA at the ends of chromosomes, consisting of long stretches of short, repetitive DNA sequences.

TESTOSTERONE

The major male hormone, produced primarily in the testes.

TRANSGENE

A gene from one organism inserted into another. A mouse carrying such a gene is referred to as a 'transgenic mouse'.

WERNER'S SYNDROME

A syndrome characterized by premature ageing, usually starting in the twenties.

Main sources:

Kyriazis M. (2005). Anti-Aging Medicines. London: Watkins Publishing

International Longevity Center ILC workshop report "Is There An 'Anti-ageing' Medicine?" (2001): http://www.ilcusa.org/_lib/pdf/pr20011101.pdf

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The 21st century technological development is revolutionizing medicine and health care, bringing new hopes to human suffering by offering cures and treatments which were unthinkable a few decades ago. This is where anti-ageing medicine finds its niche.
Anti-ageing medicine aims at slowing, arresting, and reversing phenomena associated with ageing by merging biotechnological innovation and engineered solutions. Ideally, by means of the newest medical technology, the 'body machinery' should be kept fit and at peak performance all life long. Early detection of age-related dysfunction should thus be 'fixed' at any age with interventions such as metabolic fine tuning, enhancement, regeneration, restoration or replacement of 'body parts' (i.e. organs, skin, bone or muscle). It covers a vast array of domains: from cell therapy to pharmaceutical interventions, from bio-surgery to aesthetic surgery, from human enhancement to fortified food, from smart housing and robots to toxic-free environments.
Anti-ageing medicine holds promises but also significant risks and safety issues which are addressesd in this book. It presents the latest scientific evidence on what works or does not work. It also provides public policy recommendations to ensure the protection of consumers and their rights while encouraging research and development.
This book is intended for academics, health professionals, business persons, consumers and policy-makers interested in the latest evidence and ethical issues about anti-ageing medicine.

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