Something to chew on

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Something to chew on

delivered on the occasion of his retirement as
Professor of Biological Health Sciences in particular Human
Nutrition, at the Faculty of Health, Medicine and Life
Sciences at Maastricht University on 6th June 2014.

Valedictory address
by Wim H. M. Saris

Dear Audience,

First of all, I am amazed and humbled by the number of people who have travelled from great distances to participate in this event. It is a great honour for me to welcome you all to Maastricht.

The title of my lecture “Something to chew on” is the title of a book on the challenges and controversies of Food and Health that Mike Gibney, a good colleague and friend of mine from the University College in Dublin, wrote a few years ago¹. He wrote the book over a couple of years whilst waiting in airport lounges for his next flight. Using his title with permission will certainly raise the question: “Chewing on what?” The answer of course, has to do in part with what I have done at Maastricht University since 1982, and in part with my other interests and activities. This title has also given me the opportunity to discuss a few completely different topics since that is what we do in our daily lives: chewing on a large variety of food products with different tastes and textures: sometimes sweet, sometimes bitter.

Being appointed as professor in Human Nutrition means that nutritional sciences has been and still is the main focus of my work for the past 32 years. We have to study the effects of specific nutrients on our health, and secondary the mix of nutrients within food products that is composed of sometimes very special diets. In particular in the lay press nowadays, we often get the feelings that we only have to deal with these special diets.

Recommended Daily Allowances

‘Studying the intake of nutrients in relation to health’ means in the first place discussing ‘how much do we need from a specific nutrient for optimal health?’ or our Recommended Daily Allowances. Reason that RDA’s will be my first chewing topic for today.

Besides that, RDA’s took a considerable part of my time as chairman for 15 years of the RDA committee (Normencommissie) in the Dutch Nutrition Council, this later became a part of the Dutch Health Council, and another 8 years later as the Scientific Committee on Food of the European Commission in Brussels, nowadays known as the European Food Safety Authority (EFSA) in Parma. I have to commit that this was not the most exciting part of my career: having long discussions about RDA’s. Before telling more, it is good to give some historical perspectives of the origin of RDA’s, especially today, this 6th of June. RDA’s are essential for the evaluation of the quality of food intake as well as for the planning

of food supply. In fact, planning was also the starting point for the development of RDA's during the Second World War. The US Army asked Ancel Keys to study the needs in term of energy and nutrients for soldiers landing in Europe and who had no food supply for at least one week. This resulted in the so-called K-rations used during the landing in Normandy, which today makes it exactly 70 years ago.

Later on, Ancel Keys was asked to study how to re-feed subjects after severe starvation as the Allies already knew at that time about the situation in the concentration camps in Poland. The two books Keys published in 1950 about the "Biology of Human Starvation" are classics in the field of energy needs and are real science with a great impact.²

Ancel Keys continued his work looking into the nutritional needs and initiated in the sixties of the so-called Seven Country studies about Diet and Heart Health, leading to the famous Mediterranean diet and the general RDA to reduce saturated fat. My colleague and friend Daan Kromhout, who took care of the seven country legacy, recently set up a website with all the results from over fifty years of epidemiological nutrition research (www.SevenCountriesStudy.com).

One of the research sites was in Crete, more specific a rural farmer area with a very traditional diet with a high olive oil intake. It is of interest to mention that a few years ago, a student of mine, Constantine Vardavas, did his PhD-study on the nutrition and physical activity in the valley of Messara, the same region where Ancel Keys collected the data of what became the famous Mediterranean diet. Today, over 45 years later, not much is left from this famous diet: farmers move around in the fields on their quads and have a steady diet that does not differ much from what is eaten over here or in the US, except for the olive oil.³

The data Ancel Keys and his team collected in the forties and fifties about the amounts of energy, vitamins and minerals are still the basis of today's current RDA's in most countries.

In the last 50 years, a system has been developed to determine the RDA of a specific nutrient for a population or for specific groups, such as pregnant women or infants. Based on the mean requirement plus two times the standard deviation, we have defined that a set of RDA's should be sufficient for at least 97.5% of the target group. Next to this level, we have also put in place procedures to determine the levels of safe intake, the so-called the Tolerable Upper Intake Levels (UL) as well as the NOAEL and LOAEL levels for no adverse effects levels and lowest adverse effect levels. This sounds robust with not too much trouble to get a fair figure. However, when putting this into practice, scientists judge differently over the same studies.

Let us take vitamin D for instance. As part of the European EURECCA project, Esmee Doets from Wageningen University collected all existing RDA's on vitamin D for the different age groups in Europe.⁴ Large variety of RDA's were observed with at times extreme high or low values in the age group of 9 months.

Diversity in vitamin D recommendations for males in Europe. (Doets et al. Ref. 4)

This large range of RDA's is not specific for vitamin D, as you can find this for most other nutrients as well. Critical scientists say that it has little to do with science but more with politics. I agree with this opinion, given my own experience in this field. It is certainly not a part of nutritional sciences to be proud off. Hopefully, EFSA will come up with a scientific sound renewal of the RDA's in the next two years that can be used for the whole of Europe.

I believe part of the diversity in RDA's is caused by the difference in the way we think. The classical approach is to focus on deficiency prevention and prevention of diseases in groups, using the depletion/repletion model and based on disciplines such as physiology, biochemistry and pathology. In the nineties, this is shifted with the introduction of the -omic technologies like genetics, transcriptomics, proteomics and somewhat later metabolomics. I will return to this new approach later in my talk. Depending on the composition of the committee, differences

are observed in RDA's. The positive news is that with these new technologies, a revival of the vitamin and mineral research has started. Vitamin D is a good example of this revival with new beneficial effects, such as in heart disease outside the traditional bone formation function. Hence, the RDA for vitamin D started to shift upwards after decades of relative constant figures.

It is interesting to see that all the know-how and expertise on these traditional nutrients such as vitamins and minerals we had in The Netherlands has now disappeared in our academic institutes. Even on a European level, it is minimized. I do not plea for initiating a Centre of Excellence for vitamin research in the Netherlands, but we must look at the European level to concentrate this type of work. It is no surprise that I suggest the European Joint Programme Initiative "Healthy Diet for a Healthy Life" as the-place-to-be for discussing these issues.

RDA's are not only for the micronutrients. For over 50 years now, the debate is about macronutrients protein, fat, and carbohydrates contributing to the energy requirements. For the sake of time and simplicity, I left out the role of alcohol today. In his farewell lecture in 2011, Martijn Katan from Free University Amsterdam argued that diets are not 'good science' as they do not meet the basic requirements of science.⁵ Science reduces many different things to one variable, which is measurable and immutable. I agree with Martijn on this point. However, searching for the effects of one of the energy related macronutrients has its impact on the others: high fat means low carbohydrates and visa versa, which makes this part of the establishment of RDA's difficult, if not impossible.

In the sixties, the cholesterol raising effect of saturated fat became clear in the scientific community and next to the replacement by unsaturated fat, the spur to move to less fat and consequently more carbohydrate were a logical step. This sounded not only as a logical step in relation to cardiovascular disease, but with the increasing prevalence of obesity -in particular in the US during the seventies and early eighties-, it was believed to help maintain the energy balance as well. Already for two decades, RDA committees decreased the fat recommendations from 40 En% to 25 En%. With some delay, the industry followed the advices from the nutritional sciences and created in nearly all sectors, low fat alternatives with similar taste patterns. So, problem solved? No.

For the cardiovascular health outcomes, it turned out not to be the best recommendation as low-fat high-carbohydrate diets lowered not only the bad LDL cholesterol but also the good HDL cholesterol.⁶ The advice

was to increase fat intake and have a better ratio between saturated and unsaturated fat. From a cardiovascular perspective, a lower carbohydrate intake was mandatory. Also, more importantly, the figures of fat and carbohydrate intake on one hand and the prevalence of obesity on the other showed that we as nutritionists were completely wrong. The so called “American paradox” became visible: a clear decrease in fat intake was observed, based on the food surveillance studies both in the US and later also in Europe; yet on the other hand, the prevalence of obesity was not stopped. On the contrary, the rise was steeper as never before. From that moment on, the nutritional sciences started to lose credibility and the era of diet gurus started. Confusion was completed because who were to believe?

In this period of worldwide confusion about what to recommend, we were interested in the type of carbohydrates and their role on energy intake and weight control. Today, we would talk about the glycemic index. High glycemic carbohydrates give an immediate rise in blood sugars and low glycemic food gives a slow rise in blood sugars. Personally, I still do not like this approach of functional differentiation in the types of carbohydrates since it does not reflect real life. Many interacting food ingredients such as fat, leads to blood sugar levels differently than expected compared to the ingestion of a single food ingredient. Reason why I coordinated the first European prospective intervention study CARMEN -acronym for CARbohydrate Management in European National diets-, funded by both the EU and the European Sugar Association.⁷ The fact is that the sugar industry which co-funded this project turned out to be of great impact when the moment came to publish the results of this first large scale RTC on the effects of type of carbohydrates on weight control. Most probably for this reason but difficult to prove, medical journals like NEJM and The Lancet, were not willing to accept our paper due to the outcome that the differences between sugary and starchy diets were not that significant at all.

In the CARMEN study, we looked at the effect of a reduction of fat intake with 10 En% and at the same time, an increase in ratio between simple carbohydrates or complex carbohydrates from the usual 1 to 0.5 or 1.5. A 10 En% fat reduction was included in the design study, merely because the loud message from cardiovascular-oriented scientists was to increase fat intake despite the fact that animal work already clearly showed that a higher fat, and ad-libitum intake -voluntary as much as you want diets- increased body weight. So, our first hypothesis was that a reduction of fat intake in ad-libitum diet leads to weight

reduction; however, a decrease of fat content automatically leads to an increase in carbohydrates. Our second aim was to focus on the types of carbohydrates: simple or complex. I have to confess that this aim was also driven by my personal irritation that well-known nutritionists talked about fat and sugar in one breath as being the energy dense factors in our food and being equally bad for your body weight most probably not knowing that there is a two-fold difference in the energy content per gram. CARMEN was also the first diet intervention study in which a 'laboratory supermarket system with barcode reader system' was used to determine exactly which products were taken home. The use of this system made it possible to keep subjects on their specific diet. For instance, low fat–high complex carbohydrates for many months compared that you offer all prepared foods in a box. It is obvious that people want to make their own decisions on what to eat and our system is now frequently used all around the world. The outcome of this study was not a great surprise. Indeed, reduction in fat content of the diet lead to weight loss as expected. In that same period, Astrup, Hill and myself published a meta-analysis on the reduction of fat content in a diet under free-living conditions with the same overall effect of about 2.5 to 3 kg weight loss per 10 En% fat reduction.⁸

More of interest in the study was the finding that the type of carbohydrate did not have any significant effect on weight although the more unrefined carbohydrates seemed to give a somewhat better outcome. Nevertheless, the pressure on increasing the fat recommendation did not reduce. So, let us focus for a moment on this so-called American Paradox. Indeed, the figures from the NHANES data on fat intake show a steady decline over the last 20 years while levels of obesity prevalence inversely increased during that same period.

Here, we face another inherent weakness of the nutritional science: we completely depend on the reliability of the subject's food intake records. It is well known -based on the precise Doubly Labelled Water technique- that energy intake is underreported by subjects with higher BMI. Consumers know that fatty and sugary foods are not the healthiest ones to select, as that has been educated for decades now. Most probably as a consequence of this, subjects unconsciously forget to write these foods in their food diary. With the stable isotope technology, Klaas Westerterp and his group from our department in Maastricht showed very elegantly that obese males are considerably underreported in particular fat intake. Also calculations based on the food production balance sheets from the US and Europe on the production of edible oils from 1965 till 1998 per

capita, show that there is a considerable increase of approx. 25% over the same period when consumers reported lower fat intakes. The food availability figures recently published by Carden and Carr show a similar pattern.⁹

Of course, one could say that consumers throw away more food as the costs of food are decreasing, but it is difficult to explain the American Paradox completely based on the increase of food waste.

Macronutrient availability per capita in the US (Carden and Carr. Ref. 9)

Therefore, the intake of fat is most probably not decreased over the past decades and it is still valid to come with a recommendation of lower fat intake in relation to body weight control.

As stated earlier, our interests in the interaction between nutrition and genes started to grow at the end of the last century, and it was the next step to include logically in the next European project called NUGENOB. This time, Thorkild Sorensen from the Institute of Preventive Medicine in Copenhagen coordinated it. The NUGENOB acronym stands for NUTrient-GEnE interaction in OBesity. In this European multi-centre intervention trial with 800 subjects, we decided to study more specifically a high-fat

/ low-carbohydrate vs. a low-fat, high/carbohydrate diet. This time under a very well controlled energy reduction regime of minus 600 Kcal per day for 12 weeks measured and clamped on the individual energy needs. Important argument for this design was still the on-going discussion about the role of fat and carbohydrate on energy metabolism and weight control, given a specific genetic make up of the individual. The outcome was reassuring that calories from fat or carbohydrate are still calories in relation to energy balance. Both groups lost identical amounts of weight over these 12 weeks hypo-energetic diet of minus 600 kcal per day.¹⁰ It also strengthened our ideas that a lower fat recommendation of around 25 En% is the best in relation to body weight management. At that same time, the high fat 'Atkins diet' became extremely popular. So you can imagine nutritional scientists were not taken very seriously at that time in the media. In the Atkins diet, both fat and protein are high in content. Already for years, it was known that in the hierarchy of satiating power per calorie, protein scores much higher compared to carbohydrates and certainly compared to fat. This strengthened the idea to design another large-scale multi-centre intervention trial to study the effect of extra protein in a diet. At the same time, the popularity of the glycaemic index of food became stronger as an important factor in the prevalence of obesity and type 2 Diabetes, although large-scale intervention trials were lacking on the effect on weight control.

After nearly two years of preparation, the European DIOGENES project was born. It was the largest consortium ever in Europe, containing 34 partners from academia and industry working together on Diet, Obesity and GENES. DIOGENES was chosen as acronym. Core activity was the dietary intervention study in eight European countries, in a multi-factorial design high vs. normal protein intake; high vs. low glycaemic index; next to a controlled diet based on national dietary recommendations were tested. For the design of this study, I choose the well-proven concept of weight maintenance success after a short-term weight loss period of about 10% body weight using the concept of low calorie diets. We had developed this study protocol over the years, testing different food ingredients and lifestyle interventions. After weight loss, individuals are much more prone to regain weight. This design gave us the opportunity to test much faster whether a new ingredient or concept would work. The outcome of the dietary intervention on weight maintenance was accordingly as we hypothesized: a higher intake of proteins in combination with low glycaemic foods turned out to be the best combination to maintain the body weight loss.¹¹

Personally for me, the DIOGENES project was the final part of a long journey gathering scientific arguments about the ideal macronutrient composition in relation to weight maintenance. It also gave me plenty of opportunities to work further on the genetics of weight control. I will return to the issue of genetics and nutrient sensitivity at the topic of personalised nutrition.

Diogenes study: weight changes (kg) over 6 months with a high or low protein (HP/LP) and high or low Glycemic Index (HGI/LGI) vs. control diet (Larssen et al Ref 11)

After all these years of research, the question should be raised whether we now have enough scientific arguments to come with valid RDA's for the macronutrients; protein, fat and carbohydrates. It is disappointing to say but to obtain valid recommendations of the tools to measure are crude and to verify the hypothesis in dietary intervention, studies needs too much time, efforts and funds. Some scientists proposed to go back to history and see what our ancestors were eating when we were not surrounded by cheap and well-tasted food at every street corner. Eaton has called it "Stone-Agers in the fast lane", though it may be reasonable to assume that nutritional requirements, which are relatively

universal across human population, were established in pre-historic times.¹² although emerging genomics has raised some question, it is still acceptable to assume that our current gene pool is adapted for foods consumed during these stone ages. Paleo-anthropological research into human diet evolution, drawing on analysis of preserved remains and materials and using today's isotope technologies, gave a fairly good picture of the diet in the stone-age about 50.000 years ago. These diets were based chiefly on wild game, fish and uncultivated plant foods. They provided abundant protein; a fat profile much different from that of our affluent Western nations; high fiber; carbohydrate from fruits and vegetables (and some honey) but not from cereals, refined sugars and dairy products and high levels of most micronutrients. Calculation of the average macronutrient intake shows an interesting picture of a relative high protein intake of about 30 En%; low in fat of around 20 En%; a high level of unsaturated fatty acids and 50 En% unrefined carbohydrates. These figures tend to the ones given earlier in my presentation. Low fat intake, increased protein intake leaving about 50 En% of carbohydrates. However, it is time to hand over the search for the ideal macronutrient composition to the younger generation nutritionists. Most probably, they can come with a more valid answer, having all a lot of new genomics tools available.

The New –omics technologies into the nutritional sciences.

This brings me to my second chewing point: The inclusion of all new -omics technologies into the nutritional sciences.

As a physiologist from origin, the Keystone meeting on weight regulation in the summer of 1994 in Copper Mountain, USA was a turning point for me. It was the first Keystone meeting on Diabetes and Obesity Metabolism and many rumours were going on about a breakthrough in the physiology of body weight control. Three months later, it turned out to be the paper in Nature by Jeffrey Friedman about the discovery of leptin using positional cloning of the mouse obesity gene.¹³ In 2006, I had the honour to award him with an honorary doctorate from our university. Now Friedman is on top of the list for candidates to receive the Nobel Prize for Medicine. His paper in Nature was a real turning point in the research on the interaction of nutrition and body weight control. Long time ago, it was Hippocrates who wrote that the obese should eat only once a day and takes no baths, sleep on a hard bed and walk naked as long as possible. Hardly, any progress was made on this up to the nineties of the last century. With the new –omics technologies

in hand, it became possible to open the black box called 'body weight regulation'.

If we want a better insight of how nutrition affects metabolism and health, we should have an ménage a trois of physiology, genetics and molecular biology. In 2000, this resulted in the first project, I initiated under the umbrella of the IOP Genomics called: 'An integrated genomics approach towards gut health'; a collaboration of 6 nutrition oriented institutes in the Netherlands.

In 2002, Michael Muller from Wageningen University initiated the Centre for Nutrigenomics under the umbrella of the Top Institute Food and Nutrition (TIFN), as part of the Netherlands Genomics Initiative. In 2003, Ben van Ommen from TNO-Zeist and Fre Pepping from Wageningen University started the European NUGO organisation. In this way in a relative short period of time, we were able to implement the -omics technology into our nutritional research in the Netherlands and take the lead in Europe. Now 10 to 15 years later, all this is routine and we are facing new challenges.

The Diogenes project is a fine example of showing all omics technologies integrated in a dietary intervention study in order to search for genes and biochemical pathways to find out who are successful in weight maintenance and who are not. Next to the standard phenotypical clinical data set containing the classical information on food intake; anthropometry; blood biochemistry; lifestyle; behaviour questionnaires and specific challenge tests like the standardized meal test, we have collected data on gene variation measured by the so-called Single Nucleotide Polymorphism analysis using a Genome Wide Analysis approach. We measured gene expression in adipose tissue that was originally done by the traditional micro-arrays technology. Recently, a grant from the EU gave us the opportunity to sequence the samples completely. Furthermore, proteomics on all blood samples and finally metabolomics on blood metabolites including lipidomics were done. All by all, it has grown to a database at terabyte level. It is the 'world of big data' and it leads to a complete new discipline called "System Biology": integration of all available information in order to see whether it is possible to detect differences in metabolism. For nutritional science, it will hopefully give a better insight in the nutritional needs as well as the metabolic consequences of a specific diet. So, how to handle these huge data sets is now on top on the agenda of most institutes. It is good to know that last year Maastricht University started the Maastricht Centre for System Biology MaCSBio with the funding two projects for 1.5 M€ each.

Our Diogenes database will be used for further analysis in the SYSTOPP project along with the Nestle Institute of Health Sciences in Lausanne, Switzerland.

The use of these enormous data sets poses both great opportunities and significant challenges in highly inter-disciplinary research projects. The future will learn whether the nutritional sciences will benefit from this development.

Personalised Nutrition

This brings me to my third chewing point: 'Personalised Nutrition' - since we are all different.

Already at the start of the last century, nutritional science was well aware of the importance of genetics in relation to nutritional health status. Thus, the inherited disorders of metabolism, such as phenylketonuria (PKU) clearly showed a relation between a genetic abnormality and the influence of a diet. Another obvious example is lactose intolerance, which is a condition resulting from an inadequate production of the enzyme lactase in the small intestine due to genetic variation in the lactase gene. Lactose intolerant individuals are unable to breakdown lactose from dairy products. As a consequence, these individuals suffer from gastro-intestinal distress when consuming milk products. As a result, the individual advice is to select lactose-free products or use lactase supplements. The variability between individuals in response to dietary intervention based on genetic variability, was firstly described in 1977 when the effect of the common polymorphism of ApoE on disorders of lipid metabolism in men was described.¹⁴ Those who carried the Apo E 4/4 alleles had a considerable higher risk for lipid disorders and cardiovascular diseases. The effect of diet modification such as reduction of total fat by carbohydrates on HDL cholesterol levels can differ significantly between individuals as shown in the Framingham study based on the gene variants of the hepatic lipase gene.¹⁵ This variability in response to dietary intervention is a well-documented phenomenon in nutrition research and practice.

Predicted HDL Cholesterol linked to the different gene variants of the hepatic lipase gene as a function of the total fat intake (Ordovas et al Ref 15)

The differences partially account for the limited effectiveness of the one-size-fits-all population based dietary guidelines for health promotion. Some individuals benefit more by following different dietary recommendations based on their individual genotype. This approach of personalizing dietary advice based on 'responders' and 'non-responders' is one of the primary goals of personalised nutrition.

The announcement of the first working draft on the human genome on June 26th 2000 was a historical landmark in biological research. At the same time, it created hype for possibilities to achieve everything we ever hoped for from a medicinal point of view. Hence, it was no surprise that in the academic and industrial nutrition and food sector, this announcement too sparked hope to give a much more precise dietary advice to individuals. In 2000, Sciona started to provide health and nutritional recommendations based on an individual diet, lifestyle and a unique genetic profile. Sciona was a company with scientists that were working together with the best experts in academia and was engaged with regulatory authorities. Unfortunately, it went bankrupt in 2008. In 2005, I started an important new activity at that time, within DSM nutrition R&D section: the so-called emerging business area Personal Nutrition. Thus, the main reason was to see whether in 5 years time, it could bring new business to the company. We spend quite some time and budget on this topic but had to come to the conclusion that the market was not ready to continue.

Why not? Well, the scientific progress turned out to be much slower and complicated than we originally thought. With an increasing insight in the complexity of the genome, the newly detected number of proven examples of genetic variants to diet and health attribute was very limited. Even more importantly, was the growing understanding that not only a variation in SNPs lead to a specific phenotype but the human genome also has a structural variation from nucleotide insertions or deletions as well as increases or decreases in the number of genes, so-called the copy number variants. A good example of this change is the discovery that individuals, whose ancestors were exposed to either high starch or low starch diets, differ in the number of amylase genes. Even more importantly, was the understanding that expression of genetic information can be altered by mechanisms that alter the chromosomal structure such as DNA methylation. Environmental influences such as malnutrition especially early in life, plays an important role in these changes as chromosomal structures can influence the expression of large numbers of genes during the rest of your life. These changes also explain why in the first 1000 days of life, an adequate nutrition is essential for a healthier life later. All these genetic alterations make an advice about what to eat complex, if not impossible. Reason why in the last years personalised dietary advice has shifted from a gene-centric approach to a focus on personalised dietary data as well as personalised advice based phenotypic data next to the genomic data.

Personal nutritional advice is of course already available for ages through the approach of dietitians in asking the client's nutritional habits and formulating their personal advice on this. Today's new developments in this field are linked to computerized systems, online projects and mobile apps that inform clients what to eat or advice what should be purchased in the supermarket. Many on-line dietary assessments are available for this purpose.¹⁶ With the help of pictures showing correct portion sizes and much more additional information about brand names etc., information reaches a certain level of accuracy for personal advice. Also, the feedback could be standardized along algorithms based on dietary recommendations and fit to the personal situation. In particular, feedback on nutrient intake based on color-coded reference values is relatively easy. The food choice is also doable but needs little more calculation and validation. Selection of food items to correct a low nutrient intake can inadvertently cause an unacceptable intake of another nutrient. Also personal preferences and dislikes can be included leading to a better adherence to the diet. Mobile phone technology

can also be used to help the individual in suggesting the best recopies and to select the right food product in the supermarket by scanning the barcode and using the stored food table data for identification of individual food components as well as the amount. In addition, the principle of making pictures before and after a meal and/of the leftovers can be applied to inform the users about the nutrient intake.

The use of mobile phone technology and e.g. a new developments such as Google glass or I-watches, poses both great opportunities and significant challenges to obtain an optimal personal nutritional advice. Furthermore, the industrial developments of so-called digital health platforms by Philips or Samsung and just this week, the announcement of Apple in San Francisco, will certainly stimulate this development. It is clear that healthy nutrition will be one of the topics.

Interestingly enough, Samsung is talking about SAMI, which stands for 'Samsung Architecture Multimodal Interaction'. When I started my PhD track in the seventies, I worked with a small size heart rate recorder using chemical electrodes to store the number of heartbeats over 24hr as a proxy for Physical Activity. This one was also called SAMI, but this was the acronym for 'Socially Acceptable Monitoring Instrument'.

The second level of personal information is to give individual phenotypic data. The best example of course is weighting by using the bathroom scale, which is present in nearly every home. With the exponential growth in electronic sensors and unlimited data storage, all types of phenotypical measurements are possible. The best known examples are the heart rate recording as a training add or measuring physical activity by accelerometers over days, weeks or even months for lifestyle advice. In the diabetes care, the ambulatory glucose monitoring devices are already part of medical care. Blood pressure measurement, sleep pattern and breath analyses are all already commonly in practice. Dry-Blood-Spot analysis is well known from the PKU control of neonates and can be extended to all type of biochemical analysis, such as vitamins and lipids. It can be easily done at home and send by mail to a central laboratory for analyses.

With the advances in understanding the metabolic responsiveness of specific SNP's to variation in the diet also, this part of the personal nutrition advice will be improved. However, it is expected that this will take more time. The basic problem and challenge is to combine an endless number of gene variants into a specific metabolic profile that will benefit from a dietary solution. This needs large cohorts with

detailed information about genetics, proteomics and metabolomics. Next to this, information about challenge tests as the OGTT as well as gene expression data in specific tissues can help to build an individual metabolic profile that will respond positively on a specific dietary solution.

Of course, there are number of ethical issues to address to as well. Voluntary genetic testing, even for nutritional advice can yield to an unfavorable outcome related to a specific disease risk. This can lead to worrying, and as such a need for ethical responsibility and support should be included in the service. Furthermore, the handling of personal data also raises several issues yet not specifically linked to the topic of personalised nutrition. It is of importance that the provided information to the individual is valid and scientifically sound. Especially in the field of genetic testing, there is an ongoing debate in particular in the USA where when compared to Europe, the market for these tests is much more developed. The decision of the FDA to ban '23andme' from the market was partly related to these ethical issues.

However, regardless of the progress in technologies or improvement in scientific understanding of the nutrigenomics, the central key factor for a successful implementation of personal nutrition is the consumer's acceptance. In a pan-European survey of nearly 6000 participants, it was found that the willingness to undertake genetic testing for the purpose of an individual nutritional advice was 27%.¹⁷ Those participants, who were aware that they had a health problem, were more favorable towards a personal advice. In the USA, the figures are more favorable with levels up to 75%. These data are encouraging for advancement in this field, both from a scientific perspective as well as from a commercial perspective.

At the moment, we are involved in a European research project called Food4me (www.food4me.org), which includes all topics dealing with personalised nutrition: business models; consumer acceptance; candidate SNP's analysis; new technologies; and ethical considerations. The core activity is a Proof of Principle study in 7 countries with 1536 participants recruited for an online intervention study at different levels (Level 0: standard country specific guidelines advice as control; Level 1: personal nutritional advice based on online collected food intake data; Level 2: Level 1 plus individual collected data weight, waist circumference, physical activity via accelerometer and some biochemical measurement collected by the Dry blood spot method; Level 3: Level 1+2 plus individual information about some nutrition related SNP's collected via buccal

swaps). An article in a general Dutch newspaper informing about the Food4Me project showed an immense interest as over 5000 people filled out the first online screening questionnaire. This gives an indication of the consumer interests in this type of personal approaches. The participants will be followed for 6 months. The hypothesis is that more personal feedback will have a positive effect on the food intake and the behavior and nutritional status. The trial was finished last March and it is anticipated that the first results will be available early 2015. Also for the food industry, new markets are possible. So far, Nestle provides personal weight loss advices to consumers based on online energy expenditure calculation and advices on slimming products. Another interesting market might be the food supplement section. These are targeting on specific groups, for example pregnant women or athletes. One can imagine that a specific supplement mix can be offered after an analysis of the personal micronutrient profile status by the DBS technology. The 'Direct life' program by Philips for a personal healthy lifestyle is based on physical activity monitors and can be linked online to a personal coach for further advice. Also as part of this commercial lifestyle program, a healthy menu planning is under development with personal input of preferences, allergies, dis-likes etc. The possibilities within the retail sector are manifold. Some of them are already offering personal dietary analysis online and an extension to healthy eating plans is a logical next step. With the increasing trend for online shopping, it is likely to expect all type of personal approaches for healthier nutrition and lifestyle for consumers and to become also the mainstream in the supermarket segment.

Industrial Funding of Academic Research

My fourth and final chewing point is the industrial funding of academic research.

Being active in both types of research organizations for the last 10 years, it is not a surprise that I give this some thoughts too as it is now even more an issue with the considerable reduction in innovation research budgets, the so-called FES funds. As an alternative for the FES funds, the government has adopted the "top sectors" policy strongly linked to N.W.O., to reserve a substantial part of its budget for research directly steered by the industry. This last decision shows the ignorance of politicians about the importance of free academic research to boost long-term innovation. I feel sorry for all those brilliant young scientists who suffer to continue their academic career due to the very limited

funds available for Veni, Vidi and Vici projects. Experience has learned us that radical innovation in industry does not come from academic projects based on existing ideas within the industry, but comes from new brilliant ideas in the academic surroundings and have a high risk of failure. Industrial oriented research is of course necessary too and until now, it was always well organized in the Netherlands within the public-private Institutes, such as the Top Institute Food and Nutrition (TIFN) within the food sector and the Dutch Polymer Institute (DPI) within the chemical sector. It was a lightning example for Europe on how industry, institutes as TNO and in particular academia can work together. However, our government decided to start something completely new. The reduction in research funds was evitable, given the economic crisis although many European countries who were hit even harder in the crisis decided to keep investments in innovation at similar levels or even higher. The Dutch decision to abandon the PPI infrastructure without any clear alternative on how to integrate academic research will draw heavily on the innovation power in our country.

Remains the question of how far academic institutions should work together with industry. All around the world, governments have encouraged university-industry collaborations for a long time with the argument to spur innovations and bring jobs, investments and life-enhancing products, such as healthier food. Then, the reduction in academic funds for research has forced the universities to collaborate even more closely with industrial companies. Unfortunately, the interaction is controversial. We all are familiar with the examples from the tobacco, pharmaceutical and many more industries, manipulating research questions and public discourse for their own benefit or even suppress unfavorable outcomes.¹⁸ For the food industry, the allegations are less severe. Lesser et al. did an analysis of 206 articles and concluded that industrial funded articles became a positive result more significantly compared to the non-industrial funded articles.¹⁹ In my opinion, this is not a surprise as industry will only fund projects with a reasonable chance of success. The conclusion that this phenomenon would potentially have significant implications for public health seems to be biased to me as well. Nevertheless, like in any other industrial sector, there are risks of coloring or even manipulating results. Transparency is the key to avoid these problems in collaboration with the industry.

More relevant was a recent comment in *Nature* from Wright whether industry-funded academic research boosted innovation or not.²⁰ Next to the concerns mentioned earlier, two major concerns related to

valorization of findings are often mentioned. Firstly, the concern that industry, while using the public funded university infrastructures tie up intellectual property for themselves. Secondly, the overly restricted university technology transfer policy stifles a productive deal making between companies and academic researchers. Some might advocate that the companies funding the research should manage a collaboration by an outside agency or directly. Given my own experiences within our university, I agree with this vision. Over a period of 20 years, Wright investigated the inventions logged by the technology transfer offices of 9 campuses and 3 national laboratories in California and came to the conclusion that within industrial funded projects, significantly more inventions were patented. As an index of valorization, the patents were also more than twice cited compared to the governmental funded patents. This is in line with the open innovation policy seen in many companies nowadays. Companies recognize the benefits of sharing exploratory research together with academia. However for the academia, it gives additional research projects that might be beneficial for many others.

The only issue left is the growing concern of consumer groups and allegations in the lay press that scientists who are involved in industrial funded projects cannot be trusted and should not serve in expert panels, such as EFSA. A consequence of this growing concern is that excellent scientists will not accept public advisory activities any more, given the risks of being crucified in the press.

Finally, I would like to say a few words of thanks.

Let me start by thanking the lecturers at this exiting farewell symposium today:

Ian Macdonald from Nottingham University, excellent scientist who was crucified some months ago in the UK tabloids; Daan Kromhout from Wageningen University; Hannelore Daniel from Technical University in Munich; and finally Rick Mattes from Purdue University USA.

Thank you for coming to Maastricht and be present here today.

I will now switch to Dutch for my final words of thank.

Allereerst wil ik de universiteit en vooral de faculteit Health, Medicine and Life Science bedanken voor het creëren van een werkomgeving waar ik 32 jaar met heel veel plezier heb mogen werken. Ik heb de universitaire werkomgeving altijd een 'prettige jungle' genoemd: 'veel eigen initiatief en niet altijd teveel aantrekken wat centraal werd gezegd of vaker wat *niet* werd gezegd'. Een jungle waarin het soms ook moeilijk werken was, gezien de soms extreme lange periodes van besluitvorming. Tijdens mijn sabbatical van maart 2003 begonnen de eerste overlegbijeenkomsten over het UMC+. Zeker voor het onderzoek binnen NUTRIM een belangrijke organisatorische verbetering. Vorig jaar, in 2013, is het initiatief formeel afgeblazen. Ook de huidige fusieperikelen binnen Humane Biologie en Bewegingswetenschappen zijn hiervan een voorbeeld. Maar het eindresultaat telt en dat is een werkomgeving creëren voor goed onderwijs en onderzoek en dat is zeker in de afgelopen 32 jaar gebeurd. Belangrijk hierbij zijn de keuzes geweest bij de start van de universiteit, namelijk het probleem-gestuurd-onderwijs en het kiezen van een beperkt aantal thema's voor het onderzoek binnen de toenmalige faculteiten Geneeskunde en Gezondheidswetenschappen. In 1992, 10 jaar na mijn aantreden, hebben we het onderzoeksinstituut NUTRIM kunnen oprichten. Collega Soeters, destijds de steunpilaar in het ziekenhuis, heeft in 2006 bij zijn afscheidsrede uitgebreid stilgestaan bij de problemen hoe een instituut te runnen dat te maken heeft met twee faculteiten en een ziekenhuis.

Gelukkig was er ondanks de organisatorische wirwar aan regels en financieringen, op de werkvloer een geweldige spirit om samen dit thema van de grond te tillen. De keuze om de onderzoeksfocus scherp te houden op humane voeding en het voedinggerelateerde toxicologie is mij zeker niet in dank afgenomen door vele onderzoekers, die juist in deze prettige jungle een eigen weg wilden inslaan. Het afgelopen jaar bleek dat de focus toch goed gelukt is in de 13 jaar dat ik NUTRIM heb

mogen leiden en de jaren daarna onder leiding van Annemie Schols want een bibliometrische analyse over de periode 2008–2012 liet zien dat NUTRIM als onderzoeksinstituut in een citatie analyse van de 5000 meest geciteerde artikelen in het domein Nutrition op plaats 6 staat, na 5 bekende nutrition research instituten, waaronder Havard. Een beter afscheidscadeau kan ik me dan ook niet wensen. Het laat zien dat door het bundelen van krachten de wereldtop bereikt kan worden. Het kostte 20 jaar om tot dit niveau te komen, het kan in enkele jaren worden afgebroken door het verdunnen van de middelen naar allerlei zogeheten ‘nieuwe profielen en innovatie thema’s’. Reden om nog eens krachtig te pleiten de onderzoeksinstituten te blijven koesteren, mede gezien de huidige discussies in het azM.

Een bijzonder woord van dank wil ik richten aan mijn 60 promovendi, waar ik zeker gedurende 4-5 jaar van hun onderzoek intensief contact mee heb gehad. Zij zijn de core van het onderzoek, ook al is het voor hen een leerperiode van het doen van onderzoek. Zonder hen zou het werk een stuk saaier zijn geweest en zeker niet zo uitdagend. Ik ben er ook trots op dat intussen 10 zelf weer hoogleraar zijn en nu eigen promovendi opleiden. Ten slotte de vakgroep Humane Biologie, opgericht door Foppe ten Hoor voor het biologische onderwijsdeel in de Algemene Faculteit en om mede te voorkomen dat de Faculteit Geneeskunde een te dominante rol zou spelen binnen Gezondheidswetenschappen. Tijden veranderen, alhoewel het nog steeds jammer is dat destijds (eind jaren tachtig) het plan van Greep en Ten Hoor om te komen tot een Faculteit Health Sciences het niet gehaald heeft en we nu eigenlijk als laatste in Nederland nog steeds worstelen om er een organisatie van te maken. De vakgroep heeft ondanks de soms grote verschillen in karakters, gezamenlijk veel weten te bereiken zowel op het gebied van onderwijs als onderzoek. Ik herinner me nog als de dag van gisteren dat vanaf “de berg” het bericht kwam dat de goedlopende opleiding Biologische Gezondheidskunde geofferd werd voor de transNationale Universiteit (tUL), in samenwerking met Hasselt. Gezamenlijk hebben we ons toen over deze bittere pil heen kunnen zetten om na verloop van een aantal jaren en het echec van de tUL zonder al te veel kleerscheuren de opleiding opnieuw op te starten. Het is jammer dat juist nu, bij het verzoek van het faculteitbestuur om te fuseren met de vakgroep Bewegingswetenschappen, het evenwicht verloren dreigt te gaan. Het vormen van eigen groepjes leidt tot verlies van kritische massa en kwaliteit; reden waarom ik er helaas vanuit ga dat het fusieverzoek uiteindelijk werkelijkheid zal worden. Voor mij was het in ieder geval een privilege om 32 jaar een bijdrage te mogen leveren aan deze vakgroep.

Gelukkig is mijn thuisfront uitermate stabiel en heb ik bij hen al sinds mijn studietijd rust en steun gevonden. Dat geldt zeker nu met de kleinkinderen Hidde en Lotte. Veel meer dan ik hier wil zeggen, ben ik hen daar dankbaar voor.

Dames en heren, we zijn gekomen aan het einde van mijn afscheidsrede. Dat betekent niet dat het ook een afscheid is van u allen. Ik ben nu zo'n 40 jaar met u opgelopen en zal dat ook in de komende tijd nog wel blijven doen. Wel steeds in mindere mate, totdat we uiteindelijk ieder onze eigen weg vervolgen.

Ik wens u allen, de faculteit; de onderzoeksschool NUTRIM; en de vakgroep Humane Biologie een goede toekomst toe.

Ik heb gezegd.

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