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Periodontics: current concepts and emerging trends

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Introduction

Future developments in the State and in the society are based on German national data. We know that we have a so-called age pyramid, which in 1910 had a very broad base of young people and a very small part of it represented the older proportion of the population (Fig. 1). Now by 2000 this had changed, where we have a major percentage of people getting older and we have a smaller percentage of young people, which is also related to developments like the pill, so that the percentage of young people in our population has decreased, and we know that by the year 2030 this will have changed even more and the majority of people in Germany will be older (1).

If we look at different models for the development of the population, even if we include a rather high percentage of migrating people coming into the country, we will be hardly able to keep the same size of the population as we have today, which is about 80 million. It is predicted that we will have a severe population decrease, going down to about 65 million people, and the percentage of people who will be in an age range where they are working, where they are adding to the benefits of the society where they are paying taxes, is decreasing. If we then add a certain percentage of unemployment then you can imagine, what will happen and how this will affect the financial situation of the State in future.

In fact we know that this overall development will not be the same in all parts of the country and some areas will experience severe decreases whilst others will see increases; like Berlin, Munich, Stuttgart, and Hamburg. In the major areas of the country, we will see dramatic decreases of the population as this has been calculated from the Federal Statistical Institute. In fact in the year 2050 every third German inhabitant will be 60 years old or older, and we have to consider these numbers if we are

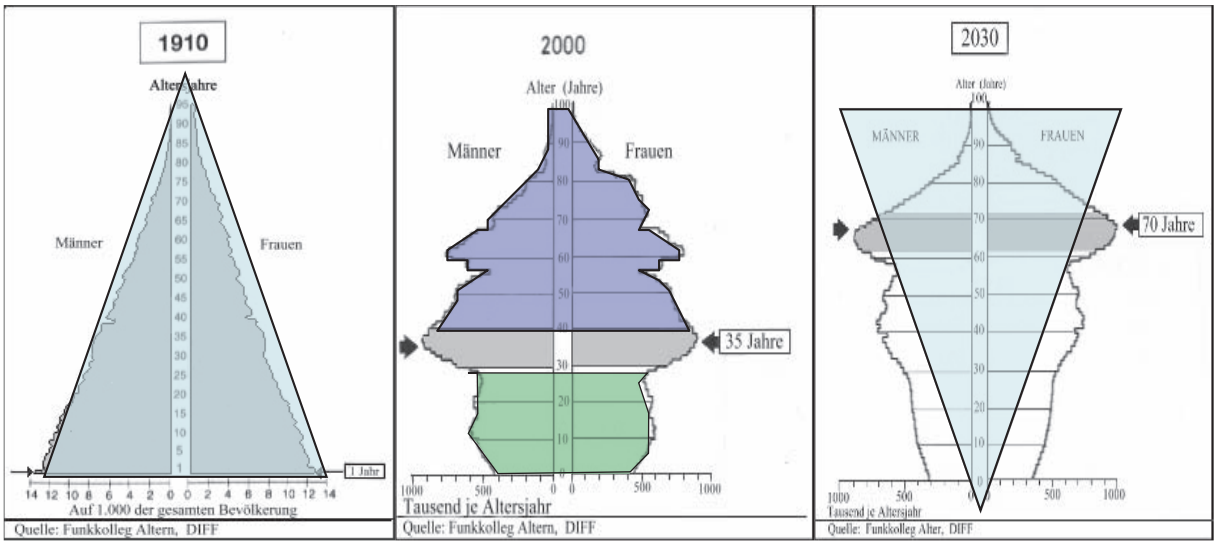

Fig. 1. Age pyramid based on national German data.

talking about the expenses, such as for health. We know that an inhabitant aged 85 years takes about five times the amount of money for health care than somebody at the age of 30 or 35.

So this is the framework in which we are living and this is something which is influencing not only the health system but the whole society. There are even shifts inside this society, and we know that certain parts of the population will increase and others will decrease even more dramatically.

Technological developments

I just want to pick out one topic to give you an idea about the developments in this area. Gordon E. Moore, who was working at the Intel company on the development of computer chips forecast the number of transistors on a single processor over the years (Fig. 2). In fact Moore predicted this development which is still correct today – he created the so called 'Moore's Law' which says that the number of transistors on a chip will double approximately every 2 years, and you know what this means with regard to computer power and calculations (2). So if we look at the millions of instructions per second (MIPS) we are up to now – more than a million – and we look at the megabytes, and we compare this with the capacity of certain brains and certain animals, and even of humans, then you see that we are rapidly approaching the capacity of the human brain (Fig. 3). It is already predicted, by the people from Microsoft, that even in our generation, within the next decades, we will see that the calculating capacity of the computers will be twice and three times the capacity of a human brain. How this will affect the whole system is not known, but the brain power in the IBM 'Deep Blue' chess computer is already at the same level as a monkey, so it is only a matter of some years or even some months where we get to this situation, and we all are aware that this will affect our daily life.

What does this mean in relation to dentistry and to periodontology? First I want to address patient management very briefly. Today if you have a patient with periodontal disease who is in maintenance, he or she possibly has to go to the dental practice every 3 months, maybe every 6 months, maybe once a year, depending upon different factors and different situations, but if we consider the developments which I just mentioned, we can readily imagine that there could be a so called 'home care system' for the patient, which takes up some information, which has the capacity to evaluate certain situations which will give feedback to the dental practice, which can monitor the patient's health state on a daily basis (Fig. 4).

Today we discuss factors where we are able to predict disease development over weeks or months, but maybe this will not be necessary. If we are able to establish daily monitoring and we see that somebody is getting into a certain risk state of the disease – inflammation for example, then the system could at least inform the dental practice, or it could inform the patient, or it could even react according to this disease state. This is no longer future, this is already a reality, but as far as I know its only a reality in medicine. If somebody has a myocardial infarction in our country, after undergoing bypass surgery, his medical care provider gives him a weighing device and a blood pressure measuring instrument, which are linked to his

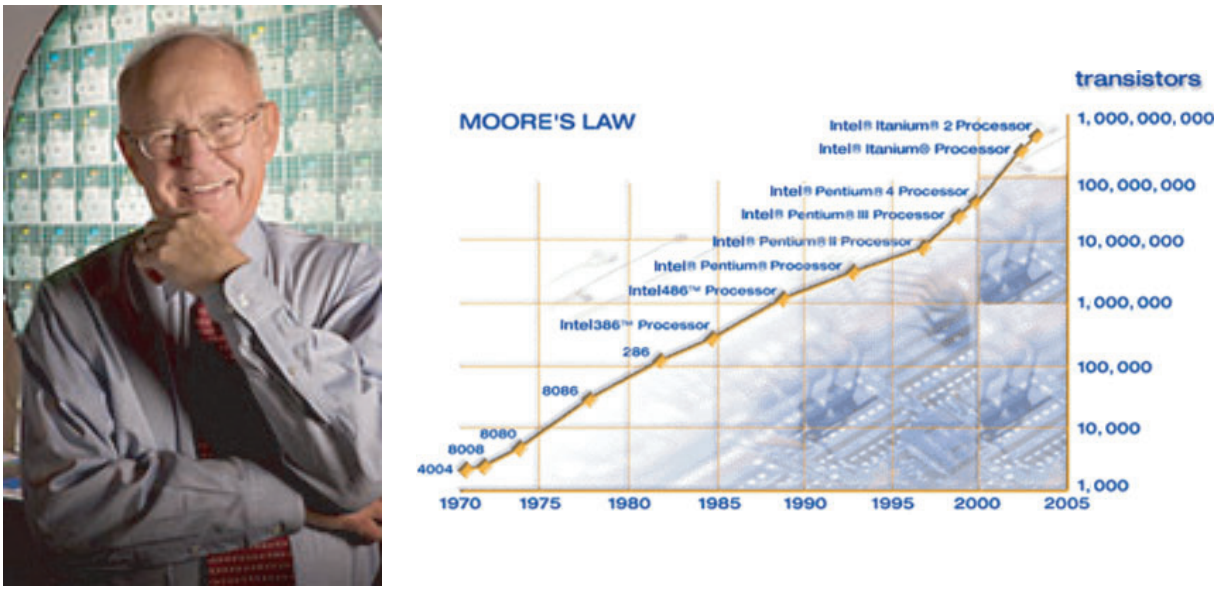

Fig. 2. Gordon E. Moore and Moore's law predicting the development in chip evolution.

phone line. Then he is asked to step on the weighing device and measure his blood pressure every morning and this is immediately transmitted to a centre where all the data are collected and compared. If the people see that there are any changes they will readily call him back and ask him to go to see his doctor. So these systems are already in use in certain areas of our country, at least.

At the last Ittingen workshop of the European Federation of Periodontology (EFP) there was a proposal discussed which stated that 'periodontitis is an inflammatory disease', and I think we have seen in several presentations here that indeed there are some aspects which underline this statement, and I was glad that Ubele van der Velden mentioned this experimental model which is now 40 years old (3). Today we know that there is a variation in the onset of gingivitis and there are people who are susceptible to the microbial attack. We know that there is also a variation in the resolution of the inflammation.

This is one of the papers which I picked out where Trombelli et al. (4) were able to identify a so called 'high responder' and 'low responder' subgroup in a total group of 96 participants who underwent an experimental gingivitis study, and still we do not know exactly what renders somebody a higher or lower responder but this could be something for future research in order to get a more clear vision about what is going on related to the microbial attack.

The current model of pathogenesis, is composed of the microbial challenge, the host response, the connective tissue and bone metabolism and the clinical symptoms of the disease, which are modulated by acquired or inborn factors (5) (Fig. 5). It is interesting to see that there are some reactions coming from, connective tissue coming from enzymes which could cause destruction and which are not related to microbial attacks.

There is one paper which came out last year in the *Journal of Dental Research* where they were looking on the proteinase activated receptor 2, which is expressed on different cell types like epithelial cells, osteoblasts and gingival fibroblasts. They were activating these receptors by gingipains from *Porphyromonas gingivalis* but also by trypsin-like proteinases (6). This activation caused in an animal model periodontitis but also exacerbates existing periodontitis. The inhibition of MHPs and cyclooxygenase decreased induced periodontitis and may be a novel approach to modulate host response. This is opening an area, which is related to the statement that periodontal disease might be an inflammatory disease. It is still questionable, if we can come back from the disease state to the health state, or if this is always going in the same direction. There are certain molecules, which have been identified during the last years, like the lipoxins. Lipoxin A4 is a potent modulator of neutrophil activity which is shutting down the neutrophil leading to apoptosis, which is modulating the macrophage so that the cell is releasing not pro-inflammatory but anti inflammatory activity, phagoytosing the apoptotic neutrophils thus shutting down the inflammatory response, and so it could well be, that some of these molecules, like the *resolvins* or lipoxins are able to protect the body in a certain way.

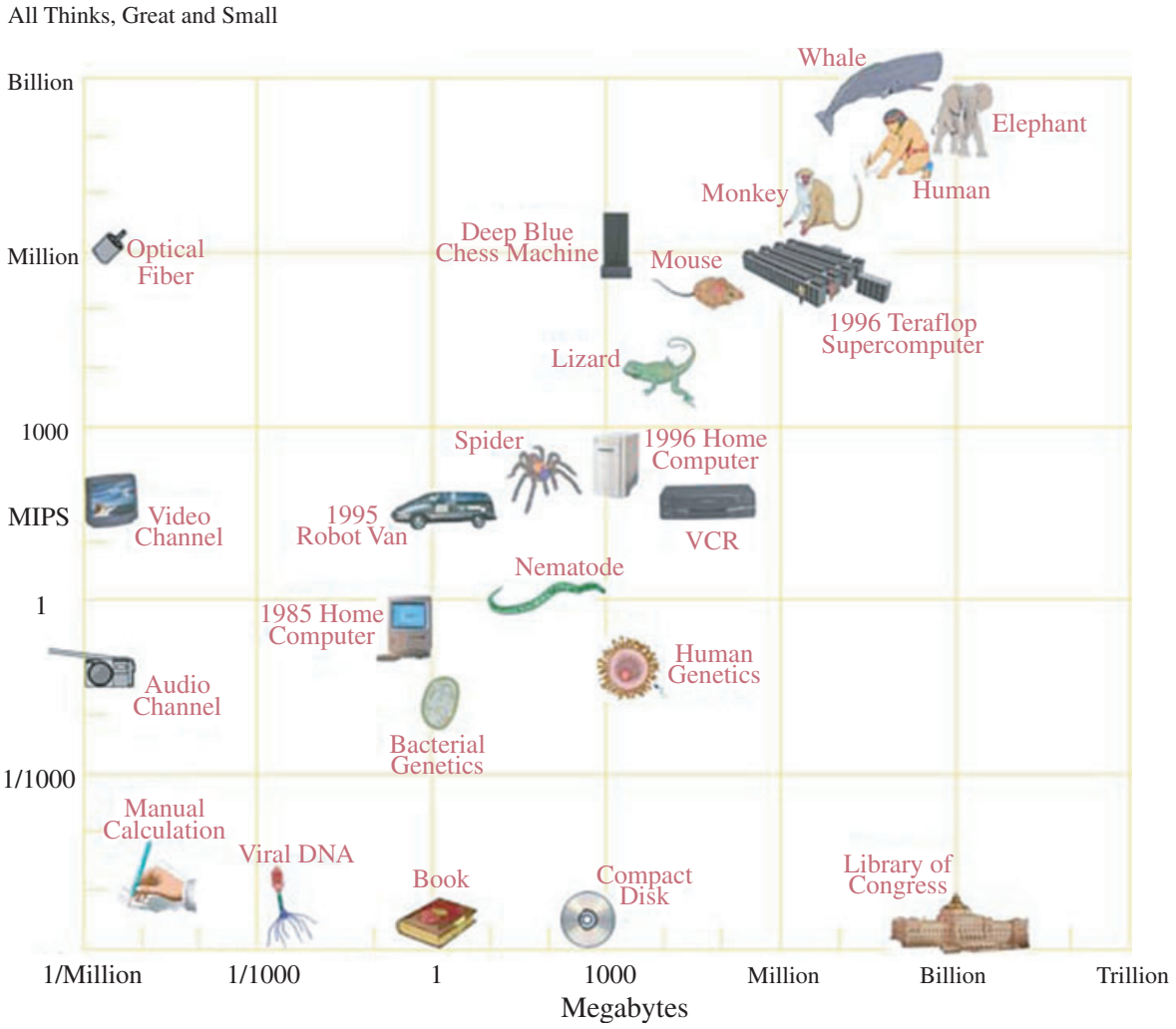

Fig. 3. Integration level of computer chips compared with the brain capacity of biological systems (MIPS, million of instructions per second).

Visions in Telemedicine

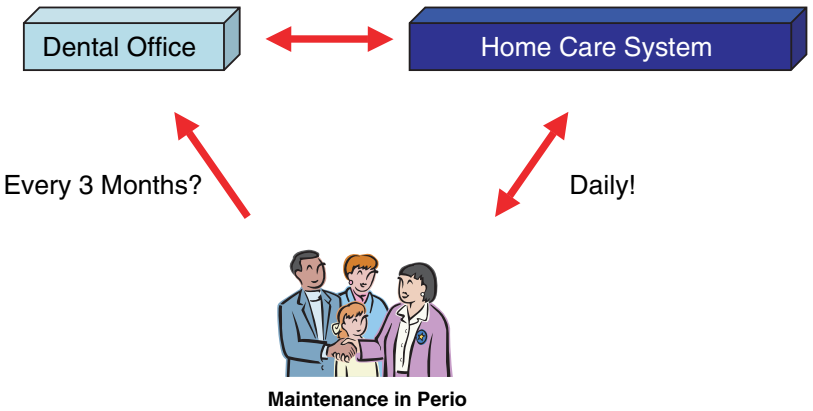

Fig. 4. Possible network in teledentistry with daily monitoring of the patients health state.

This is the result of an animal experiment which was performed by Kantarci and Van Dyke where they used white New Zealand rabbits as a periodontitis model, they introduced ligature-induced periodontitis and infected with *P. gingivalis* and then they added the resolvin E1 and the aspirin triggered a stable lipoxin E, and they were able to protect the animal

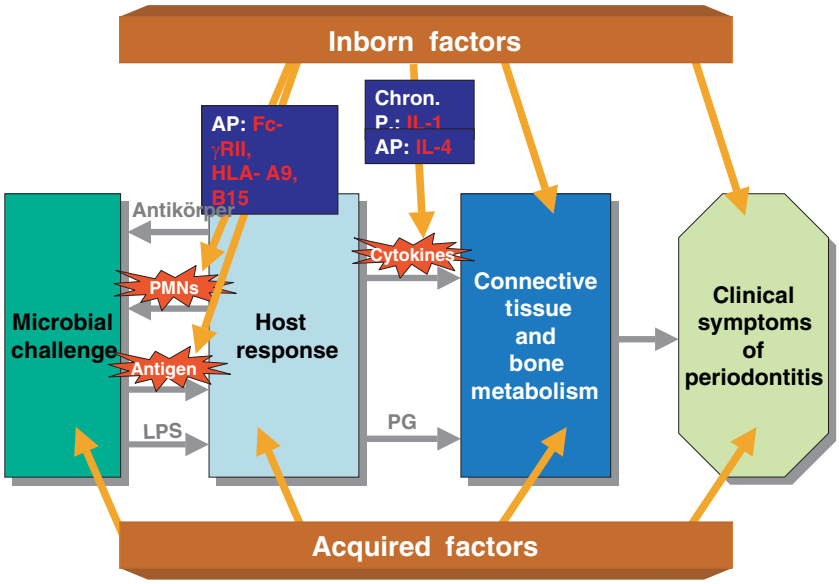

Fig. 5. Model of pathogenesis in periodontitis including inborn as well as acquired modulating factors.

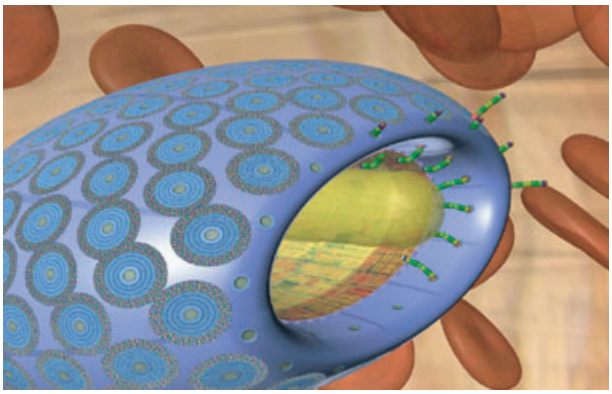

Fig. 6. 3-d model of a microbivore, an artificial phagocyte destroying bacteria without releasing proteolytic enzymes.

from periodontal disease by a topical administration of these anti inflammatory reagents. So you see that there is another side of the story, which is just coming up and I am convinced, that we will see more about this and probably this will lead to new approaches and to different therapeutic strategies (7).

Gene polymorphisms were also mentioned by Arthur Hefti and you know a gene polymorphism is a mutation which is present in a certain percentage of the population, so this has an epidemiological background, and we already have some data on different polymorphisms, but the central dogma related to DNA is that through the DNA a certain messenger RNA is transcribed which then leads to the production of the protein. Now if you go to a list published by the University of Bristol, there are >150 polymorphisms related to cytokine genes – and I am sure this has increased since I looked at it – which are all listed. If you then relate the polymorph state through a certain protein expression then at the same time there were 35 protein changes seen in 46 polymorphisms, which means that in the majority of the polymorphisms there was no clear evidence, that there was really a change in the protein products which was related to the gene which was changed. So we have to consider that the association with a certain gene polymorphism may not be sufficient and have to prove that this has consequences for the proteins which are produced (8).

There are some associations related to certain gene polymorphisms. I do not want to go into them as I know you are familiar with this and it has been mentioned by Iain Chapple this morning. However, using sophisticated DNA arrays like the Affymetrix chips we can obtain simultaneous information on thousands of gene activities at the same time. Now if we consider that there might be an interference between different polymorphisms so that the patient can have 4, 5 or 6 different polymorphisms and they may interact synergistically or antagonistically, then it is getting more and more difficult to explain the whole system, because if you have one gene we have three different possible combinations, somebody can be homozygously positive, heterozygous or homozygously negative for this gene polymorphism. Now if we have 10 different genes with these three different combinations we get the possibility of 59 049 different combinations between these gene polymorphisms and it will be very difficult to explain what is going on even though if you just consider the homozygously positive and negatives we are getting to more than 1000 possible combinations, so I am not sure if we will really succeed with this approach.

There was one interesting study which was published on human genetics in 2004, which I think is in a certain way a

hallmark study. It is related to localized aggressive periodontitis where genetic linkage analysis in four Afro-American families revealed a certain part of the chromosome 1 q 25 at the position D1 S23 238 where this region was stable, was present in all diseased members with a significant LOD score, and the haplotype analysis revealed that this was a distance of 26 million base pairs. So we know at least a certain part of the chromosome where in one certain disease type there could be something going on (9).

A new term has been coined recently, which is called 'guided pocket re-colonization', so I do not know if this will be the therapy of future and even considering the brilliant talk from Phil Marsh this morning, I do not know if we will go there. This was published in Science 2005 and was a long-term monitoring of bacteria undergoing programmed population control in a microchemostat, and the microchemostat they used had six different chambers, where the size was below that of a coin (10). This micro system worked not only for 5 h, but for some days, and they had input ports where they put in the nutrition supply channels, the waste went out, there was a peristaltic pump and a growth chamber for the bacteria. The authors were able to show that this device produced cells which were growing in different ways under different conditions. For guided pocket re-colonization using such technical devices one could imagine that there will be a system in the oral cavity which could release bacteria at a certain moment.

Coming to regenerative therapy we know that we have the Endogain® proteins and I am quite sure that we will have certain different Endogains®. These different proteins will be produced on a recombinant level, so that there will be no problem as regards possible site effects and infection.

In the field of tissue engineering, the regeneration of periodontal ligament, the production of connective tissue, the production of bone and cartilage and the production of epithelium will be possible especially since a publication appeared in the Lancet in 2004 (11). There for the first time post-natal stem cells from the human periodontal ligament were characterized and isolated from periodontal ligament of wisdom teeth of 16 subjects. The authors labelled them with two different early stem cell markers. They compared it with bone marrow stromal cells, they transplanted the cells in immune deficient rats and they differentiated the cells in various directions. When they re-transplanted the cells together with an hydroxyl appetite carrier into rats they could demonstrate the formation of a new cemental layer on top of the hydroxyl appetite carrier.

The therapy with stem cells either if these are adult stem cells or embryonic stem cells is leading to different phenotypes and different properties. We can use them for tissue engineering, bone defect repair, muscle repair, dental repair and so on, there are a lot of possibilities and options.

Coming now to the remote future for the next decades then it is getting more and more speculative and I just want to mention one point: this is nano-medicine where we are talking about nano devices in this size range, nano pores, nano dendrimeres, nano tubes, quantum dots and so on, which are below the size of a virus which is fairly below the size of a bacterium. Nano-medicine and nano-technology has recently been pushed very much in the US (12).

There is another idea about nano machines for different applications: the nano robot, which has an ATPase motor nano tubes and helical proteins (13). The device is so small, it is much smaller than an erythrocyte. Another approach used, the microbivore which is an artificial phagocyte which digests and destroys bacteria without releasing enzymes like the neutrophil (14) (Fig. 6). The energy is given to it by different systems, I do not know if it will ever be produced but the technological possibilities are improving. I do not know if they will replace the sonic toothbrush in the future but maybe they will be something in addition.

I have tried to give you some ideas of what could happen based on the current developments. There were some people stating that dentists could be the leading bio engineers in the 21st century. Our children and our grandchildren will see if this will happen. There are some very promising developments and I hope that they will help us to protect and keep the health of our patients.

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