Sowing the seeds of future success

A memorandum on the education and research profile of the Dutch UMCs

Dutch Federation of University Medical CentresForeword

Foreword

The purpose of this memorandum from the Dutch Federation of University Medical Centres (NFU) is to explain the developments in education and research at the UMCs. Its principal aim, in addition to describing the historical context and providing an overview of the current situation, is to outline our expectations for the future.

The historical survey clearly shows how scientific research in the UMCs has evolved in the last 30 years. Clinical research in the Netherlands was still in its infancy in the 1980s. Today, the Netherlands has an outstanding international reputation in clinical research , as is apparent from the fact that five UMCs were in the top twenty research centres in the most recent Times Higher Education rankings for clinical research. The creation of the UMCs has made a major contribution to the translation of research results into clinical practice, the so-called translational research. As far as fundamental medical and biomedical research is concerned, the UMCs have long performed well and their productivity is still increasing.

The UMCs, and healthcare in general, face major challenges in the near future. The proportion of elderly in the population will grow substantially. The disease burden of this segment of the population is relatively large. Until now, medical science and health care have been far better at saving lives than at increasing the quality of life. In the coming decades, medical research will have to focus on strategies to reduce the burden of (chronic) diseases and increase the quality of life, especially in old age. Luckily, new research strategies have become available through advances in the fields of high-throughput research (genomics, proteomics, etc.) and ICT, allowing a more integrative approach using large datasets. This has prompted the establishment of large data and materials banks, so-called 'biobanks'. The Dutch UMCs are among the 'biobanking' pioneers worldwide, promising useful results in the years to come. However, much of this very important infrastructure has been created with temporary subsidies. To actually reap the benefits of these investments there must be the prospect of long-term financing, to guarantee the integrity and actualisation of materials and data in the biobanks. Much can be said in favour of such a long-term commitment. A permanent research infrastructure not only supports current research, but also generates considerable research potential.

Education at the UMCs is also continuing to evolve. We recently adopted new agreements on the competencies that a medical school graduate must possess in the 2009 Framework for Undergraduate Medical Education in the Netherlands. The statutory rules on the educational requirements for doctors will be adapted accordingly.

The political demand for an increase in the number of medical students will impose enormous pressure on the quality of education at the UMCs. It remains to be seen how the high standard of education can be maintained with a growing number of students in the years ahead. On a positive note, there will be greater possibilities for local selection, an option the UMCs are keen to avail of. They also want to learn more about the factors behind successful selection of students. How can we spot good future physicians when they are just 18 years old? A final important development that needs to be mentioned is the attention that the UMCs are devoting to the development of talented students. High-quality biomedical research needs talent. Although the UMCs have created programmes for highly talented students, funding constraints prevent them from being fully utilised. The UMCs therefore call for additional investment in the development of talent. With that investment UMCs will be able to offer extracurricular training options for high-potential students earlier in their training. Talented students will then often be able to carry out doctoral research while they are still doing their training. Once they have successfully completed their training, they can become professionals in both healthcare and medical science, connecting the two. That is also in a more general way what the past decades have taught us and what we want to contribute to the 21st century: to reap the fruits of pioneering biomedical science and bring them to the growing number of patients, adding not only years to their lives, but life to their years.

Prof. L.J. Gunning-Schepers
Chairman NFU

Content

Introduction

In the context of the Ministry of Education, Culture and Science's formulation of a vision on research and education, the NFU has analysed the current status, the most important trends and the future ambitions at the eight Dutch university medical centres (UMCs). This memorandum presents a snapshot of the situation in a continuous process in which the UMCs jointly formulate a strategy in a steadily converging scientific community. After all, researchers and students come from every continent to work on problems that often also transcend this country's borders. At the same time, the UMCs have important tasks in relation to local, regional and national health care – not only in providing patient care, but also in conducting scientific research to underpin that care and of course in education and training.

This memorandum outlines the joint vision of the eight UMCs of a future full of challenges and opportunities. It is to be hoped that the audience is receptive to the most important messages in this document so that the UMCs receive the resources they need to continue meeting the challenges and capitalising on the opportunities for the Dutch patient and the Dutch economy in the coming decades.

1 | Summary – Improving quality of life

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Health care is facing major challenges: an ageing population, an increase in 'lifestyle diseases' and various other threats such as infectious diseases. On the other hand, we are experiencing a 'biological revolution' with unprecedented opportunities for health care and the economy. It is at the confluence of these two exciting developments that the UMCs gather and help to apply knowledge. If the UMCs are to maintain their strong international position in the future and find answers to the challenges in health care, there is a need for investment, particularly in the research infrastructure, based on a shared vision.

In this document the Dutch Federation of University Medical Centres (NFU) presents a vision of the future that is rooted in the past. The UMCs have established a distinct profile in the last few decades as a result of internal and external developments. The researchers at the Dutch UMCs are clear about where they stand in relation to their colleagues at other UMCs. The challenge now is to work together to find solutions for current and future social problems in the area of health and care - in fruitful competition with the rest of the world.

Challenges

The entire health care sector faces a difficult period. The number of elderly is growing (ageing), while the working population is declining (fewer young people). Since most chronic diseases appear in the second half of a person's life, this will increase the pressure on a health care system with a shrinking workforce. Up to now, the health care system has proved more capable of reducing mortality than lowering the disease burden. The number of people with nutritional diseases such as metabolic syndrome, diabetes, arthrosis and cardiovascular diseases, as well as the number of people with psychological and psychiatric problems, is growing in every age group. Then there are unpredictable diseases, such as infections, which can have a major impact on society. These health problems call for creative solutions, and scientific research is an important means of finding them. Research is also needed to guarantee the safety and (cost-)effectiveness of the solutions.

Opportunities

The results of the unprecedented advances in the medical and biomedical sciences and information and communication technology of the last half century will become increasingly apparent in the coming decades. They will lead to new ways of involving patients in their own health and recovery, innovations in the prevention, diagnosis and treatment of diseases and new ways of delivering care and information. This trend will create opportunities for Dutch companies and for the health care sector. The UMCs want to play a pioneering role in seizing those opportunities. Innovation in care and economic valorisation are priorities in current and future policy. That choice is in the interests of both Dutch patients and the Dutch economy. Having said that, fundamental medical biological research will remain an essential ingredient, particularly in the search for applications, since it has repeatedly been found in various innovative treatments, such as gene therapy and the use of stem cells, that unexpected things can occur that require one to return to the 'drawing board' and the laboratory.

Unique position

Scientific research in the Netherlands is highly competitive in relation to other countries. In some medical and biomedical disciplines the UMCs have enjoyed a strong position for years; in other areas, including clinical research, a lot of progress has been made in recent years and Dutch researchers have established a good reputation worldwide. This is also apparent from the fact that Dutch medical researchers are consistently able to supplement their budget from government funding (the 'first flow of funds') with substantial funds from the indirect funding mechanism (grants from the Netherlands Organisation for Health Research and Care Innovation (ZonMw), the Netherlands Organisation for Scientific Research (NWO) and European subsidies; the 'second flow of funds'), from charities that support research into specific diseases (the 'third flow of funds') and from companies (the 'fourth flow of funds').

An unmistakable factor in this success was the creation of the UMCs from the teaching hospitals and university medical faculties, which created powerful synergy between patient care, scientific research and education.

Consequently, the research is deeply embedded in medical practice and in society. Researchers take inspiration from clinical problems and laboratory results find their way into medical practice. This integration of the medical faculties with the academic hospitals is unique to the Netherlands. There is a constant dialogue between fundamental medical and biological research, which has traditionally been strong in the Netherlands, and clinical practice. The short lines of communication between the laboratory and the clinic create opportunities for translational research, the essential translation of research into practice. In the last few years the UMCs have intensified their cooperation and joint strategy formulation in the NFU.

Infrastructure

One tangible result of this cooperation is the String of Pearls Initiative *[Parelsnoer Initiatief]*, a project to establish a chain of so-called 'biobanks', in which data and materials relating to a particular disease are collected from large numbers of patients. Consequently, the Netherlands has also played an important role in the European Biobanking and Biomolecular Resources Initiative (BBMRI). Especially in combination with the new high throughput research strategies *(genomics, proteomics, systems biology)*, these biobanks will be an important driver of progress in the diagnosis and treatment of (chronic) diseases in the coming years. The LifeLines study, the String of Pearls Initiative and the large cohort studies in mental health care that have started in recent years thanks to the mental health programme *GeestKracht* ['Mental Strength'] also yield this combination of patient data, measurements and biological materials. With these programmes, the Netherlands has established a prominent international position in this field. This infrastructure, which can be used to find answers to a wide range of research questions, gives the UMCs a strong competitive position for securing additional funds from national and international subsidy schemes. The infrastructure is also of interest to innovative companies.

It is, however, uncertain whether the UMCs will be able to reap the benefits of these initiatives in the future. This infrastructure has been created with incidental financing and no permanent funding has been made available to maintain these biobanks: for the necessary updating of data; for the purchase, maintenance and repair of equipment; and for the basic staffing required to guarantee their survival. The same applies for other infrastructural facilities in fields such as genomics and bioinformatics.

These costs can no longer be borne by individual research projects. We are therefore convinced that a substantial, permanent increase in government funding of 80 to 160 million euro is needed to preserve essential infrastructure. With that investment, many times that amount could be raised in external financing. Naturally, the impact of the scientific findings from these projects for health care and the economy in the Netherlands is unpredictable (no one can be certain about scientific discoveries), but could easily rise to a multiple of the invested funds.

For the sake of comparison: the government funding for scientific research at all eight UMCs currently amounts to 240 million euro (roughly 15 million euro for each UMC from the central government grant for research and 15 million euro from the central government grant for teaching). They annually raise an additional 500 million euro from other sources. Investment in infrastructural projects such as BBMRI and the String of Pearls Initiative, which make the Dutch research groups even more interesting for international partners, will also increase their ability to attract funding from international companies and to secure international grants.

Sowing and Reaping

It is anticipated that the life sciences will continue to be extremely fruitful in scientific terms in the coming years. The medical and economic fruits of discoveries in this field of science will also become more apparent. The Netherlands has been a leading international player in this field for years, partly thanks to strong university groups, the creation of the UMCs and the investments made in recent years. In other words, a lot has been sown and the UMCs can reap the harvest with significant social and economic benefits.

But between sowing and reaping comes development. Developing something new takes time, particularly in the field of life sciences and health sciences. In times of financial constraint it can be difficult to make the long-term efforts needed to ultimately reap the benefits. It is, however, essential to continue making them so that care remains effective and accessible in the coming decades and to secure the social and economic 'profit'.

Talent

The international competition now extends to education as well as research. It is therefore very important for the UMCs to continue investing in the quality of education, both in medical training (which is directly related to the quality of patient care in the Netherlands) and in the more research- and policy-oriented programmes. With their international reputation in scientific research, the UMCs are currently fertile breeding grounds for talented researchers from the Netherlands and abroad. There is a lively interaction between research institutions such as the UMCs and innovative companies. Strengthening medical and biomedical education is therefore also important for the Dutch economy in the future, especially in light of the aforementioned 'medical biological revolution'. The UMCs have recently established programmes to provide additional training for talented students. However, because of the limited funds available, only very limited use can be made of those programmes. The UMCs are therefore calling for additional investment of 14 million euro a year in national biomedical education. This additional stimulus would enable the UMCs to allow their talented students to make better use of the programmes.

Conclusion

At the beginning of this new millennium the Dutch health research community is in a strong position to meet the challenges that lie ahead. At the same time, we will soon be confronted with some unmistakable problems, partly due to the ageing of the population. We want to capitalise on the high academic quality of the UMCs in terms of innovation in care and economically profitable activities. To achieve that, it is essential to strengthen and expand the current infrastructure. Facilities that need to be preserved, such as the String of Pearls Initiative, will remain vulnerable as long as no structural financing is available for the years ahead. Strategic investments are also needed in other facilities, such as imaging techniques, bioinformatics and new genome scanners. There is also still no long-term financial framework for translational research. Investment is needed in high-class education for talented doctors and researchers in anticipation of the challenges of the coming decades.

The contents of this paper

After a brief historical survey, this memorandum describes the current situation in relation to scientific research and education in the UMCs. We will then turn our attention to the future and consider the importance of cooperation and the priorities that the Dutch UMCs want to set for the years ahead.

2 | Patient-bound research and the creation of UMCs

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The university medical sector has made great efforts to meet public and political demands and expectations in the last few decades. Clinical research has improved enormously, also in the surgical disciplines. An effective system of evaluation of research and education has been put in place and the infrastructure for translational research has been put on a sound footing. The creation of the UMCs accelerated and reinforced these processes. The ensuing synergy has made an important contribution to the international success of medical research in the Netherlands.

Major changes occurred in the relationship between the government and the medical and scientific community at the beginning of the 1980s, in the Netherlands and in other countries. Developments such as the emergence of new technologies and the deteriorating economic situation led to calls for a major intensification of science policy. The government, at the time tentative and reactive, gradually adopted a more initiating and stimulating role. The government increasingly became involved in determining the basic conditions for and the direction and scale of scientific research. It was observed that there was little in the way of research policy in the universities in the Netherlands and that there was insufficient cooperation with a view to making effective use of the available research potential. Various measures designed to improve this situation were announced in the policy paper on the allocation of tasks and concentration in university education entitled *TaakVerdeling en Concentratie* ['Allocation of Tasks and Concentration in university education'] in 1982 (1) and the *Selectieve krimp en groei* ['Selective contraction and growth'] operation (2) in 1987.

Clinical research

A number of advisory reports warned that medical scientific research in the Netherlands was becoming increasingly oriented towards biomedical research, with little input from clinical research. This was clearly reflected in the financing of the research. The former Ministry of Education and Science (O&W) was an important source of subsidies for fundamental medical biological research, in the medical faculties and elsewhere, through the Netherlands Organisation for Scientific Research (ZWO, now NWO). There was no room for support for clinical research within the policy framework of this indirect funding mechanism ('second flow of funds').

The former Ministry of Welfare, Health and Culture (WVC) also felt that subsidising clinical scientific research was not its responsibility. The only real possibility for securing subsidies for clinical scientific research was in fact from the charities ('third flow of funds') and from industry to perform clinical trials. Without a change of policy, the likelihood was that the education and the quality of patient care, and hence the medical faculties and academic hospitals themselves, would also suffer the negative consequences of this situation.

Priorities in health research

These developments prompted the government to review science policy in the medical sector. In 1981, the Advisory Council for Science Policy (RAWB) was asked to evaluate current health research and to advise on improvements in the priority setting. An important question in that context was how greater and better use could be made of the research capacity to solve problems affecting public health and health care. The government also felt that research should focus more on the effectiveness and efficiency of prevention, diagnostics, therapy and organisational structures in health care. When it was published in 1983, the RAWB's report *Prioriteiten in het Gezondheidsonderzoek* ['Priorities in Health Research'] (3) for the first time gave an impression of the quality of medical and biomedical research in the Netherlands. The report concluded from the various analyses that clinical research (which encompassed roughly 70% of all research projects) was weak. The authors said they suspected that contributing factors included the way in which medical faculties and academic hospitals cooperated and were organised, the gap between clinical

and fundamental research and the leaking of research funds to advanced patient care. The report specified a number of priority areas for stimulation. An important criterion in the choice was the size of the disease burden of a particular complaint in relation to the Dutch research capacity.

In its position paper in response to this advisory report, the government largely endorsed the RAWB's analysis. In the government's opinion, the management of the medical faculties was not strong enough and the principle of distributive justice was dominant in making policy choices. Too much weight would be given to the interests of a large group of mediocre researchers.

Health Research Promotion Programme

The Health Research Promotion Programme *[Stimuleringsprogramma Gezondheidsonderzoek – SGO]* (4) launched by the Ministries of Education and Science and Welfare, Health and Culture at the end of 1985 took much of its inspiration from the RAWB's advisory report. Two actions were undertaken. First, the ministries strengthened the infrastructure of the universities by supporting ten leading groups, identified by the RAWB, which concentrated mainly on fundamental medical and biomedical research. Second, a powerful boost was provided for clinical research into complaints causing a high disease burden. This research was partly intended to lay the foundations for medical treatment and medical education (a trend that is now known as *evidence-based medicine*).

An evaluation carried out in 1998 (5) showed that the SGO had, among other things, given a powerful impulse to clinical research in the academic hospitals, across the medical and surgical spectrum. Even the surgical disciplines, in which there was less of a tradition of scientific research, were now clearly developing clinical research programmes.

With hindsight, it is possible to say that the time was right for research into a number of specific, primarily chronic, complaints with new research technologies. This stimulus, together with the establishment of university chairs and attention to education and training of junior doctors, general practitioners and specialists dovetailed perfectly with the core mission

of medical faculties and academic hospitals. The programme was also productive because those institutions were also willing to accept their own responsibility and take measures of their own to bolster the stimulus provided by the government.

From Investigative Medicine to Health Care Efficiency Research

Since 1998 medical faculties and academic hospitals have also received government grants to perform clinical scientific research from the Fund for Investigative Medicine *[Fonds Ontwikkelingsgeneeskunde]*, which was managed by the former Health Insurance Council (now the Health Care Insurance Board, CVZ). For the last ten years that fund has been continued first as part of the Health Care Efficiency research programme ['DoelmatigheidsOnderzoek'] of the NWO's Division for Medical and Health Research, and later by ZonMw. The aim of this programme is to promote patient-bound research into methods and techniques that could eventually have significant medical, financial, organisational or ethical consequences. Here too, important changes have occurred over the years. The Investigative Medicine programme, in which academic hospitals have played a positive role, was almost exclusively a 'bottom up' programme.

When the Health Care Efficiency research programme was established in 1999, the Ministry of Health, Welfare and Sport specified the policy themes on which research should focus. The academic centres were given a greater task in arranging the diffusion of the know-how acquired to other practitioners. Together they pursued this aspect of their mandate with enthusiasm, since the centres themselves were increasingly aware of the importance of listening carefully to the wishes and needs of the public.

Quality assessment: Discipline Reports on Medical and Health Science Research and BAGO 3

In the 1980s and 1990s the Royal Netherlands Academy of Arts and Sciences (KNAW) thoroughly analysed the quality of medical research, recommending improvements where necessary, resulting in two Discipline Reports on Medical and Health Science Research (6, 7), the most recent of which appeared in 1999. These advisory reports provided an overview and quality assessment of almost all medical, biomedical and health research in the Netherlands and contained very useful information for advisory bodies and the government. Quality assessment of research and of training and education has now become an integral management instrument of the UMCs.

Particularly relevant for university medical research is part 3 of the *Advies Brede Analyse Gezondheidszorg (BAGO 3)* ['A broad analysis of health care'] (8), a report that appeared at the beginning of 1995. This report showed that there was room for improvement in both the substantive effectiveness and the organisation of this research. It said that the care provided in academic hospitals should be more closely linked to the scientific research (fundamental and clinical) and to the education and training of medical professionals in order to provide better guarantees of the relevance of research and training for care in practice and enhance the interaction between and integration of fundamental and clinical research. It concluded that the administrative integration of medical faculty and academic hospital in a university medical centre would be the logical counterpoint to this construction. The government adopted most of these conclusions and stressed the importance of a strong and dynamic academic sector in a good system of health care. In 1998, it further observed that strengths of the system were the quality of research and the export of knowledge and technology.

Creation of UMCs

The former medical faculties and academic hospitals pressed ahead and formed eight UMCs that clearly reflected the government's desire to delegate responsibility in the academic sector as far as possible to the implementing parties. It is now apparent that the envisaged administrative cohesion in the strategies of the UMCs has largely been achieved and that the combination of (advanced) patient care and scientific research has greatly improved the cooperation between clinical and non-clinical researchers. Researchers at

every level generally address issues in the domains of diagnostics, treatment and prevention in multidisciplinary teams. Meanwhile, the UMCs have continued to devote as much attention as ever to fundamental research, which is after all the basis of future innovation.

Consequently, the creation of the UMCs has established a firm foundation for what has now become known as translational research (the previously missing link between fundamental and clinical research), as well as for the associated infrastructure. Research that is, incidentally, only really possible thanks to the thorough training of doctors and other medical professionals.

In short, the UMCs form a whole that is greater than the sum of its component parts. The clinical, biomedical and translational research of the UMCs has acquired a prominent position in the world. Each of the UMCs has its own profile, but all see it as their core task to make a contribution to innovation and improvements in public health and health care through research, training and education. The choices made and the coordination and cooperation at national level through the NFU are seen as an important bonus in that regard.

ZonMw: strengthening innovative research

Around the time that the medical faculties and academic hospitals were being transformed into UMCs, a parallel development, also unique in the world, was occurring in the subsidising of research and innovation in care. This was the creation of the Netherlands Organisation for Health Research and Development (ZonMw) from *ZorgOnderzoek Nederland* (ZON, Health Care Research) and the Medical Sciences division of the NWO. The strength of this organisation is that it embraces the entire spectrum of the innovation process from fundamental research up to and including the application of the results in practice. Consequently, its programmes have tremendous social relevance. There is also a greater chance that the results of research will be applied in practice and that practical problems will permeate the world of research.

The demand for social relevance can, however, lead to a short-term vision and so eventually slow actual innovation. ZonMw's principal clients are the Ministry of Health, Welfare and Sport and the NWO. The NWO's share in ZonMw's total budget is relatively small, which suggests that the pendulum may have swung too far since the 1980s. Whereas critics at the time felt too much money was going to fundamental research, the budgets for applied research in the cure, care and prevention sector have since grown strongly, while various cutbacks have been made in fundamental research.

The innovative strength of the medical sector would benefit if more money were made available for ZonMw's NWO-financed Open Programme. This is a 'bottom up' programme in which, in addition to social relevance, scientific quality is the most important criterion. It has been apparent for years that this programme has been unable to accept applications of a very high standard because of the limited resources. Increasing the budget for this programme would therefore represent a powerful impulse for fundamental innovation.

The NFU makes an urgent plea for an increase in the first flow of funds so that the UMCs themselves can establish new lines of research and will have a platform from which they can secure additional financing. Unfortunately, the opposite trend has been apparent in recent years.

3 | Quality, profiles and diversity

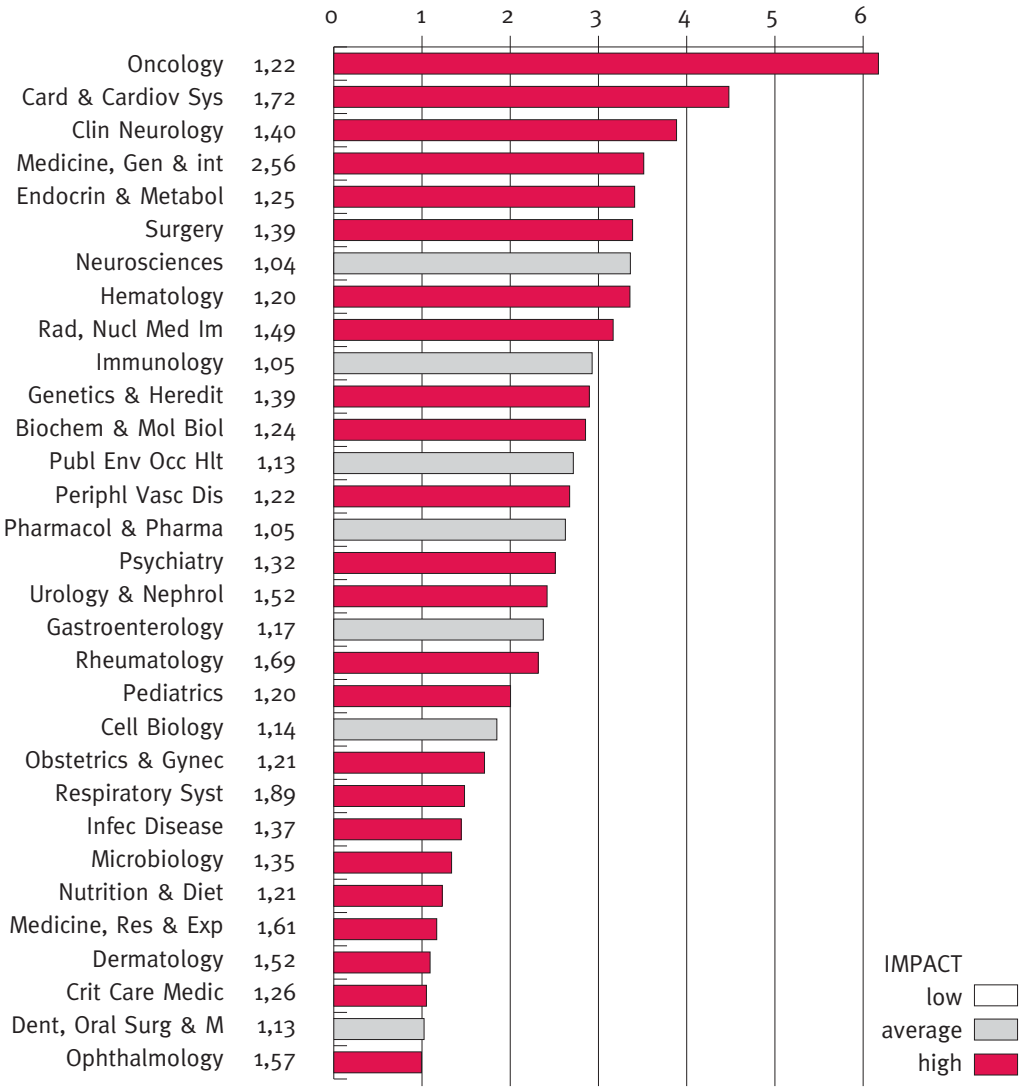


Figure 1: Research profile of the UMCs for the period 2004-2008. The profile shows the releative size (length of the bar, number of publications) and the quality (citation score). Disciplines that account for less than 1% of the total output of the UMCs are not shown. The disciplines in this figure together account for 78% of the output of the UMCs.

3 Quality, profiles and diversity

The international prestige, social relevance and economic impact of scientific research are the results of a consistent science policy in the last few decades. Meanwhile, there has been growing cooperation and joint strategy formulation. In independent analyses, medical and biomedical science in the Netherlands as a whole scores 40% above the global average. In a number of clinical disciplines Dutch medical and biomedical researchers are among the very best in the world. The research has diversified in recent years and clinical research has improved, which is part of the reason why the social impact of medical research has increased.

Analyses by the Centre for Science and Technology Studies (CWTS) have repeatedly shown that the UMCs conduct a lot of scientific research and that the standard of the research is high (9, 10). With around 8,000 scientific publications a year, the UMCs account for roughly a third of the total Dutch scientific output. In almost all medical disciplines, from fundamental to clinical, Dutch medical researchers score well above the global average. The overall score of the UMCs on citations was 1.40 in the period 1998 - 2008; in other words, across the spectrum they performed 40% better than the global average, which is almost entirely determined by publications in Western countries. Zooming in on the individual disciplines, in several areas the performance of the UMCs is world class (Figure 1), while in the majority of disciplines they perform above or well above the global average.

The analyses show that the quality of the research in general is good to very good. In a number of areas, the UMCs perform to an exceptionally high standard. This is apparent, for example, from the relatively large number of leading articles published by the UMCs. For example, 66% more of the very best publications, or the 1% of most frequently cited articles worldwide, come from Dutch UMCs than one might expect on the basis of the number of publications. In some specialist areas the citations of Dutch studies exceed the average for other Western researchers by more than 400%. There are some areas, such as virology, stem-cell research, migraine and blood coagulation, where Dutch researchers are among the twenty most frequently cited scientists in the world.

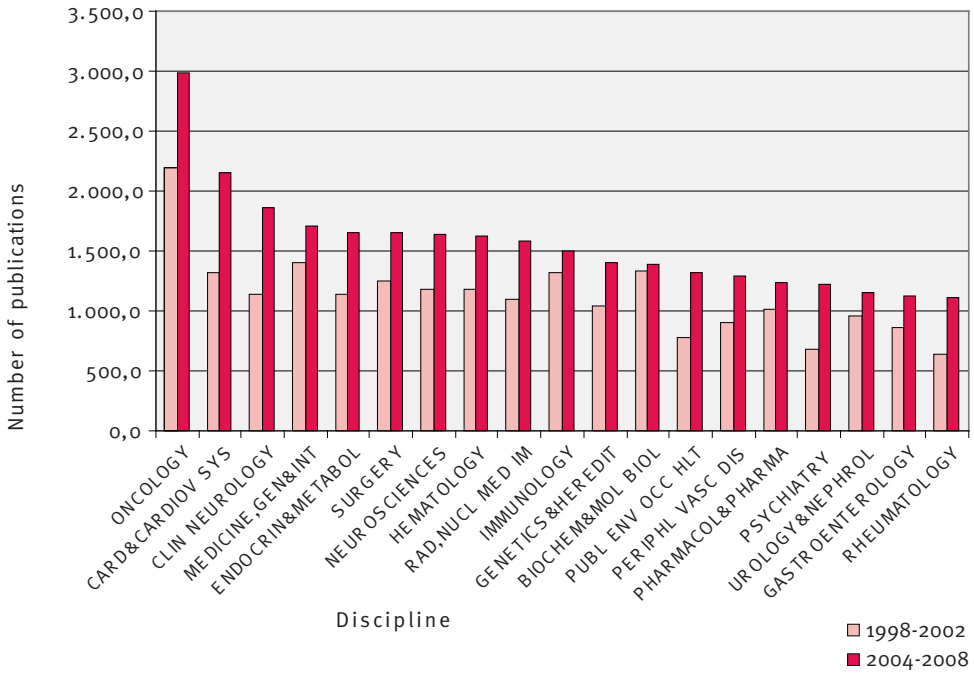


Figure 2: Distribution of research over the major disciplines for the periods 1998-2002 and 2004-2008.

Recent European comparative surveys have shown that clinical research in the UMCs is of great quality. Five of the eight UMCs are in the Times Higher Education list of the top twenty European research centres for clinical medicine, with one of them ranked first and three others in the top 10 (see http://www.timeshighereducation.co.uk/story_attachment.asp?storycode=406694&seq=2&type=T&c=1).

The entire spectrum

Figure 2 presents a list of the most important areas of medical and biomedical research for all of the UMCs. The first column covers the period 1998-2002, the second column the period 2004-2008. Broadly speaking, the figure clearly illustrates that the research covers the entire spectrum of medical and biomedical research. Research is now conducted in all relevant fields. This is very important for progress in medical science and for the availability of expertise for top-class patient care. The figure also illustrates that there has been an increase in the scientific results across the board. There is in fact a clear demarcation between the UMCs. Where there does appear to be overlap it is in broad disciplines within which each UMC makes its own unique contribution to the research. The fact that there is scarcely any overlap is in principle already apparent from the high scores in the professional literature, since 'more of the same' will not secure publication in journals like *Nature* or *Science*. Originality is also a decisive criterion for securing Dutch and European subsidies and for acquiring patents. The eight UMCs also function as a single UMC at eight locations in that sense.

National and global cooperation

Figures 3, 4 and 5 illustrate the cooperation between the UMCs themselves and the cooperation of research groups within the UMCs with other research institutes. The size of the circle relates to the number of articles and the distance of the circles from each other relates to the degree of cooperation. Where circles overlap, the cooperation is very intensive.

Figure 3 illustrates the cooperation between the UMCs themselves and with the 17 centres with which they collaborate most intensively.

Source: Converis, on the basis of the joint publications database managed by the CWTS.

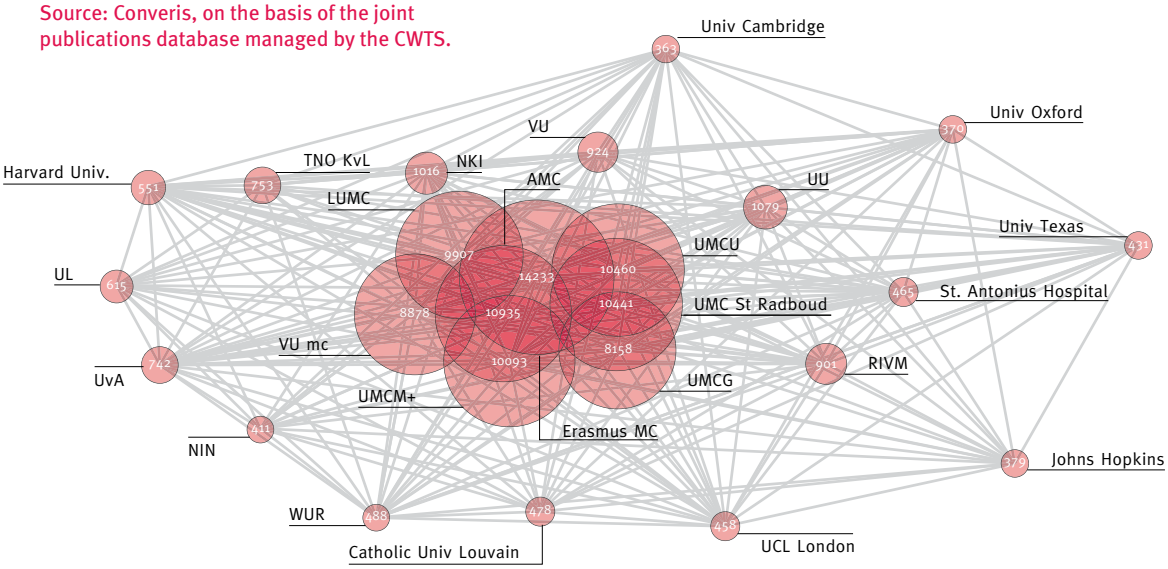
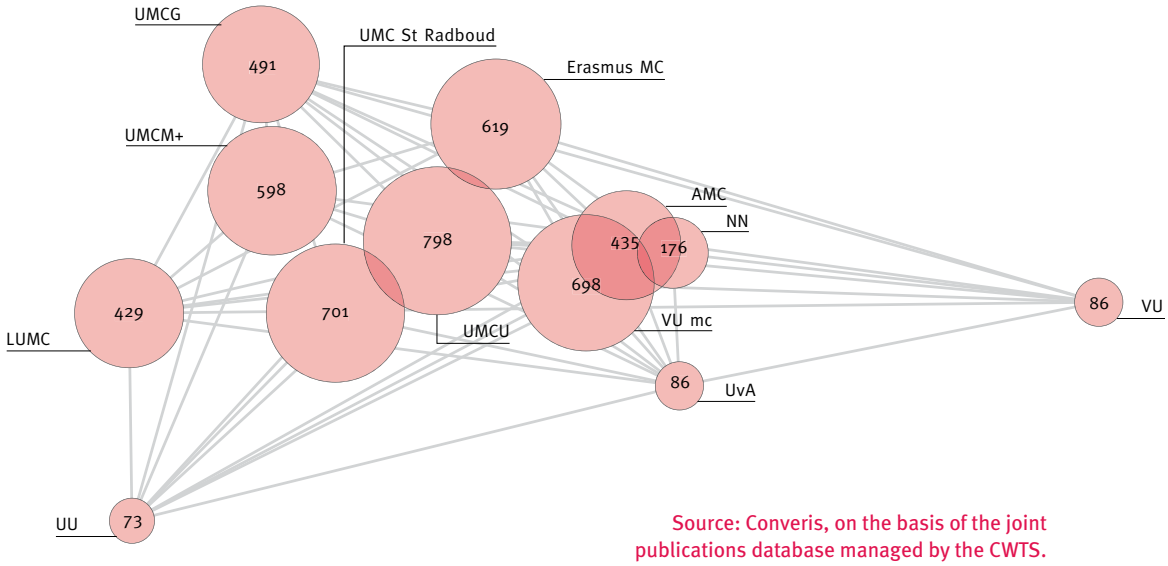
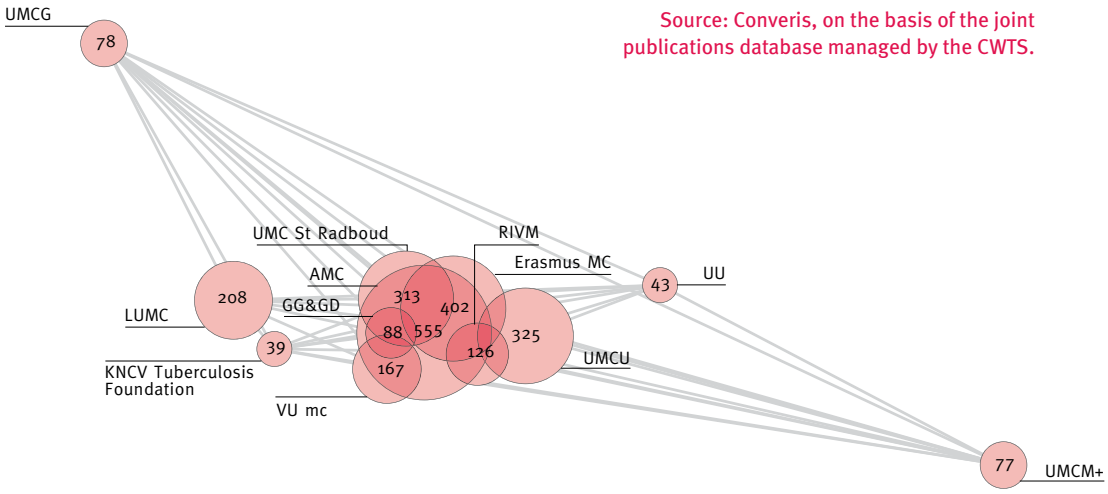


Figure 3: Cooperation relationships for all research in the UMCs.



Source: Converis, on the basis of the joint publications database managed by the CWTS.

Figure 4: Cooperation relationships in the neurosciences.



Source: Converis, on the basis of the joint publications database managed by the CWTS.

Figure 5: Cooperation relationships in the field of infectious diseases.

The cooperation is shown on the basis of all scientific articles published by the UMCs in the period 1998-2007. The proximity of two circles correlates with the number of joint publications. The figures in the circles give the number of publications: the figures in the circles for the UMCs show the total output, for the other centres they give the number of publications published with the UMCs.

What is clear is the intensity of the cooperation between the UMCs themselves (considerable overlapping of the large circles) and their cooperation with TNO, the RIVM and the universities in the Netherlands. Dutch medical and biomedical researchers are also popular partners for renowned institutions abroad, which is reflected in the close cooperation with prestigious institutions such as Harvard, Johns Hopkins, the universities of Oxford and Cambridge, etc.

The cooperation between the UMCs is greater in some disciplines than in others. Figure 4 shows the top twelve UMCs in terms of publications in the field of the neurosciences.

Figure 5 shows the top twelve institutions in terms of publications in the field of infectious diseases. There is evidently more cooperation between the UMCs in this discipline than in the neurosciences.

Medical science and social issues

Scientific quality and high scores in the international league tables are one important measure of success, but medical researchers also want to help find solutions for socially relevant problems relating to health and disease. It is therefore good to see that the clinical research in the Dutch UMCs now also measures up to the best in the world and that the cooperation between clinicians and fundamental scientists has intensified in recent decades. The creation of the UMCs (see also chapter 2) has therefore clearly borne fruit. Clinical research makes a contribution to day-to-day practice in health care as a whole: evidence-based medicine and evidence-based practice. The research in the UMCs consequently helps to improve the quality of care, promotes innovation in care and increases the competence of care professionals. This is very important for the social relevance of medical and biomedical

research in the Netherlands. Experts from the UMCs play a role in drawing up guidelines based on the available evidence. They also participate in a large number of relevant networks and are members of organisations that help the government to prepare and formulate policy, including the Health Council and its various committees. The quality of the research also directly and indirectly enhances the quality of the education, in other words the training of the care professionals and researchers of the future (see also chapter 4).

In short, the research in the UMCs not only yields publications in the leading professional journals but also responds to developments in society and public needs. This is confirmed by the report of the Advisory Council on Health Research entitled 'Research that matters. Responsiveness of university medical centres to issues in public health and health care' (11). More information about the CWTS analyses and the contributions of the UMCs to innovation in care and valorisation can be found in the NFU's brochure *Wetenschap gewaardeerd* ['Science valued'] (9). The UMCs are furthermore developing methods to highlight the contribution made to society by scientific research more clearly and make it more transparent.

Creating value

Naturally, valorisation, or the translation of research into applications, is also socially relevant. It generates economic value and enables discoveries to be further developed and to be applied in patient care. The UMCs therefore regard valorisation as one of their core tasks. In the last few years the UMCs have all formulated policies to promote the creation of economic and social value from scientific knowledge. Every UMC has its own Technology Transfer Office (TTO), which serves as a centre of expertise and actively approaches researchers and companies on issues relating to intellectual property and the commercial application of knowledge. In 2009, the NFU published a joint vision document on valorisation entitled *Naar een goede waarde* ['Creating value from research'] (12).

Leading technology institutes: from impulses for cooperation to a structural programme

The UMCs have played an important role in the establishment of a number of leading technology institutes in the last few years, including TI Pharma, the Center for Translational Molecular Medicine (CTMM) and the Biomedical Materials Institute (BMM). The government's investments in these institutes have given an important boost to scientific research in the relevant fields (development of medicines, translational molecular research, biomaterials) and have led to the creation of public-private partnerships between research institutes and companies. The funding of these top institutes will come to an end in the coming years, which raises the question of whether it should be continued. The NFU feels that it is important to continue stimulating research in those areas in the future, preferably on a structural basis. As recommended in the policy document 'Partners in the polder' (13), it is important to preserve continuity in the policy on innovation in the life sciences. The UMCs also welcome the trend towards closer public-private cooperation. In the forthcoming period, however, it will be necessary to consider carefully what organisational structure will best guarantee that scientific quality is optimally stimulated while further promoting cooperation with the business community. Since ZonMw, NWO and SenterNovem already possess expertise in these areas, the NFU favours delegating that role to those organisations.

The UMCs carry out their activities and formulate their strategy in the context of the wider consideration of the importance of the life sciences for the economy in the 21st century. The vision document 'Partners in the polder' (13) identified significant opportunities thanks to the strong position of Dutch research institutes in the life sciences. The report therefore recommended providing continuity in innovation policy for the next 15 years in order to build on the strengths that have been developed in recent years and positioning the Netherlands as a single promising bioregion with the potential of matching regions such as the Bay Area in California. That is a very ambitious objective that the NFU warmly endorses.

However, a term that often arises in the debate about the life sciences in the Netherlands is 'knowledge paradox' (innovation paradox). In the past the prominent position of Dutch scientists in the international professional literature has not been adequately reflected in valorisation in terms of business activity in the Netherlands. For example, the Netherlands has not played a decisive role in the increasingly large-scale pharmaceutical industry in recent decades. But that does not necessarily mean that the country will remain on the sidelines in the future. The medical technology of the future will impose different demands. Intensive collaboration between the laboratory and the clinic and the close involvement of specialists will be essential, especially in the development phase. This is where there are opportunities for the Netherlands. The UMCs want to seize those opportunities, naturally in cooperation with partners in the private sector and with other research institutes such as TNO. This will depend, however, on the availability of sufficient funds to maintain the infrastructure for research as well as greater scope for the funding of projects in the area of translational research.

Conclusion

The UMCS are in a strong position thanks to the scientific quality and the existing policy of promoting social relevance and valorisation. In the coming decades the scientific research at the Dutch UMCs will increasingly have to provide solutions for structural problems relating to health and care. The challenges in the coming decades are beyond the scope of an individual UMC. Cooperation and coordination will therefore be essential if they are to address these major social issues. This is a subject we will return to in the closing chapters of this report.

4 | Investing in talent

4 Investing in talent

The UMCs have a tradition of providing high-class education for medical students based on widely accepted training requirements and quality criteria. Every student of medicine consequently has the opportunity to become a good doctor. But this ambition is under pressure from the political demand to increase the number of students. A positive aspect is the expansion of the possibilities for local selection. Many UMCs are also involved in the training of other professionals in care and prevention, researchers and/or policy makers. Growing attention is devoted to early recognition and encouragement of students with exceptional talent, since anyone who starts conducting research early in his career can make a greater contribution to the progress of science.

As in the case of scientific research, the education at UMCs is ultimately dedicated to helping the patient and society. Future doctors, researchers, policy makers and other professionals, such as dentists, must be provided with the necessary knowledge and skills. The scientific knowledge acquired should ultimately benefit the largest possible number of patients. In medical programmes a lot of attention is also devoted to communication and other skills. Medicine is, after all, the art of healing, a discipline that is rooted in scientific theory and evidence but at the same time imposes high demands on the practitioner's non-cognitive skills and dedication. It is also important in this context that prospective medical school graduates and medical specialists are already introduced to the concept of life-long learning from the first year of their course so that they continue to meet the standards of quality demanded by the professional group and society in the practice of their profession.

In this chapter we first discuss the medicine programmes. They have only limited scope to pursue local ambitions and capacity and demand are crucial factors. We then discuss specialist programmes and other courses in which there is greater local variety.

Medicine: quality, supply and demand

Medicine has traditionally been a very popular course. Those who choose to study medicine are often highly motivated, which is reflected in the high success rate. It is often talented pupils who choose to study medicine. Students who enrol for medicine achieved a high average grade in their final exams in pre-university education (VWO) (14), a trend that is undoubtedly also encouraged by the fact that students with an average grade of over 8 in the final school exams are exempted from having to participate in the lottery to allocate places in medical programmes.

In the past the popularity of medicine prompted a series of policy measures that have always led to debate: the numerus fixus, the lottery and the privileged position of candidates with a grade higher than 8 in the final VWO exams. A new element has entered this discussion in recent years and that is the question of whether these measures are appropriate for ensuring that students admitted to a programme will ultimately prove to be good practitioners. The theory behind the numerus fixus, a quota for the number of students admitted to a medicine programme, is that medicine is different to other courses because the prospects for a medical school graduate (not to mention a Bachelor's graduate in medicine) in the labour market are limited. Only students who are able to secure a place in one of the specialist courses have the prospect of a job in the future. It was and still is felt to be socially irresponsible to train students for long-term unemployment. An additional factor is that medicine is a relatively expensive course, especially in its current form with a lot of small-scale education.

The lottery is the increasingly controversial instrument used to implement the numerus fixus. In the current social climate it is no longer regarded as acceptable that factors that are necessary for professional practice, such as an individual's school performance, motivation and personal characteristics, do not count in a person's chances of being admitted to study medicine. As already mentioned, as far as school performance is concerned the law has already been amended. The majority of the UMCs assess other factors, such as motivation, themselves. The NFU would welcome expansion of the statutory possibilities for local assessment and selection, so long as it does not become mandatory. That would also provide a unique opportunity for

scientific research into the effects of new methods of selection for admission on the quality of those who ultimately graduate from medical school. Recent Dutch research suggests that selection otherwise than by lottery could help to reduce the number of students that drop out of the programme and possibly also increase the quality of graduates (15). It is important to continue this research and to investigate different forms of selection in different curricula.

Because of the ageing of the population, but also other factors such as doctors working shorter hours, the demand for well-trained general practitioners, medical specialists and other doctors is growing. The NFU supports the idea of adapting the numerus fixus to this growing demand for doctors. But such an increase in the number of first-year students and in the number of students progressing from the basic course must then be matched by the possibilities for entry into the advanced programmes. An increase in the numerus fixus will in itself require a logistical tour de force on the part of the UMCs, since providing high-class education on a small scale demands well-trained teachers, as well as classrooms, ICT capacity, etc. The principal bottleneck in the Master's phase is the clinical capacity. The UMCs and the affiliated hospitals have very limited possibilities to increase the number of medical interns. Unbridled growth in the number of medical interns would lead to an unacceptably low standard of clinical education and cause disruption of patient care.

The UMCs feel that the complete abolition of the numerus fixus, as called for by some politicians, would create far more problems than it solves. Apart from the aforementioned logistical problems in the education, there is the risk of creating a huge pool of medical school graduates with no prospect of progressing to advanced courses. An additional fear is that the quality of the students being enrolled will decline if students who choose medicine no longer have to meet any criteria. When personal performance, motivation and quality are no longer decisive for admission to the programme, the success rate in medicine programmes will very probably decline sharply.

For these reasons, the NFU feels that abolishing the numerus fixus would be a disastrous move and expresses the hope that no such step will be taken. The alleged benefit, that it would reduce the shortage of medical specialists, can

be achieved far more effectively by engaging in a dialogue with the advanced medical courses. By contrast with the training of medical school graduates, the primary responsibility for this lies not only with the UMCs but also with organisations of medical specialists and general practitioners (scientific associations).

The Council for Public Health and Care (RVZ) presented its advisory report on the numerus fixus to the Ministers of Health, Welfare and Sport and Education, Culture and Science on 29 January 2010 (16). The RVZ called for the abolition of the numerus fixus. One of the conditions it stipulated was that the government should exercise control by providing funding for a specific contingent of training places. According to the RVZ, abolishing the numerus fixus implies the abolition of the lottery. Specifically, the proposal means that the number of medical students to be admitted will be fixed locally and that there will be considerable scope for local selection. The NFU broadly agrees with this.

Statutory training requirements

The content and form of the education of future doctors have changed substantially in the last few decades. Whereas 30 years ago most of the education in Dutch medical faculties still consisted of lectures, with a curriculum that maintained a rigid separation between subjects, the structure has gradually become smaller in scale, with a more cohesive, problem-oriented approach. All Dutch medical students have benefited from the modernisation of the system through the cooperation between the UMCs.

There has also been structural consultation on the training requirements for the profession of doctor since the beginning of the 1990s. Since it should not make any essential difference for a doctor or his or her patients which UMC the doctor graduated from, anyone who passes their medical exams in the Netherlands should possess the same competences. These competences are legally prescribed in the form of requirements for training. The blueprint for these requirements is the Framework for Undergraduate Medical Training, which was adopted by all of the UMCs in 1994. In mid 2009 the NFU executive commissioned a revision of the framework to take account of the latest insights into medical science, social changes and medical education.

The curriculum for the basic medical course is based on the competences defined for the advanced courses for medical specialists. This helps to guarantee the quality and effectiveness of the training continuum. Another fundamental innovation in the 2009 Framework (17) is that medical training has been brought into line with the Bachelor's/Master's structure as agreed by the European Ministers of Education in the Bologna Declaration in 1999. In response to signals from the advanced courses, the new Framework also gives renewed emphasis to the basic subjects, since these form the context within which clinical phenomena have to be interpreted. The 2009 Framework for Undergraduate Medical Training was published on 12 August 2009 after it had been presented to the Minister of Health, Welfare and Sport. The minister is preparing an amendment to the Decree on the Training Requirements for Doctors that will correspond with the new framework.

The framework is not only important for establishing uniform national requirements for medical training. It is also the ideal frame of reference for the periodic external review of the quality of that training and marks an important point in the medical training continuum encompassing university medical training, advanced medical training courses and permanent education.

'Couleur locale' and international

The requirements laid down in the framework create a rigid structure that leaves little scope for local variants. Nevertheless, some UMCs want to allow more scope to establish distinctive profiles within those basic conditions in the coming years. This applies for both the Bachelor's and Master's courses. For example, some offer an English-language curriculum targeted at students from other countries and Dutch students who intend to practise as doctors mainly outside the Netherlands. Some UMCs also have teaching hospitals abroad.

Some UMCs have a relatively large percentage of students from outside the European Union. Research is currently being conducted into the admission, progress and graduation of these students in medical courses, with the aim of improving the success rate of these students. Although the expectation is that many of these students will return to their country of origin after graduation, some will proceed to the advanced courses. The UMCs devote

special attention to people who have qualified as doctors outside the European Union and have come to the Netherlands as refugees. Another group that receives special attention are students who enter medicine after completing all or part of a related programme such as biomedical sciences.

Master's phase in medicine: the balance between university and general

The central feature of the Master's phase of medical training is the practical training as an intern. Less than half of this education is given in the UMCs; most of it is given in general hospitals and other care institutions in the region. Every practical situation offers unique opportunities for the trainee professional. In a UMC, with its emphasis on top reference care, research and education, the prospective doctor learns different things than in a general hospital, where the emphasis is on common ailments.

The organisation of this education has changed a lot in recent years. There is consultation between the UMCs and their affiliated institutions in the so-called Education and Training Regions. This new structure has smoothed the transition from the training as medical school graduate to advanced courses. It has also created a platform in which UMCs can address various issues such as capacity, efficiency, quality control, managing waiting lists and establishing and maintaining skills labs.

All programmes are working on quality

The UMCs devote a lot of attention to the quality of the education and the teachers in both the medical courses and in the other subjects (see also below). As far as the students are concerned, it is important that they are enthusiastic about the course and their future profession and feel sufficiently challenged so that they can develop their talents and the success rate of the course is optimal. This applies for the Bachelor's and Master's programmes and – for medical students – for the advanced medical courses. For teachers and trainers (training teams), education must be appealing and challenging.

Incentives for talent

The powerful position occupied by the UMCs in the field of scientific research and high-class patient care has a positive effect on education, training and further education in various ways. This attracts talented individuals from the Netherlands and abroad, both teachers and students, to the Dutch UMCs.

Students with exceptional talent are increasingly encouraged to combine research and medical practice at an early stage in their study. The so-called honours programmes, which practically every UMC has in one form or another, have proved extremely fruitful. The interaction between studying and conducting one's own scientific research appears to work well with those who possess the necessary talent. It is often a way of encouraging individuals to start a doctoral project while they are still doing their medical training. They can later bridge the gap between the worlds of patient care and scientific research and between different scientific disciplines. Acquiring a research mentality at a stage when a person can still oversee the full extent of the domain produces a type of researcher that is badly needed in current practice: with a broad orientation on the one hand, while focussed on personal expertise on the other.

Two UMCs currently offer four-year Master's programmes for doctor/clinical researcher. These courses are open to select group of students with a Bachelor's degree in biomedicine. The programmes meet the requirements set out in the framework and so comply with the Decree on the Training Requirements for Doctors. At the same time, these courses are designed to provide the students with a higher level of competence in the skills required for medical scientific research than are acquired in the regular medical training. In addition to these programmes with the focus on research, there are also other programmes that offer extra possibilities for the students, such as honours/master classes and other Master's programmes such as clinical epidemiology.

The intensive supervision and longer duration of the study make these dual programmes relatively expensive. Looking to the future and the need to train sufficient doctors/researchers and to strengthen the link between fundamental and clinical research, it would also be desirable for the UMCs to

have a structural budget for training these talented people. Broadly speaking, the period of study is extended by roughly three years. The additional costs for each student who follows such a dual programme are 180,000 euro. The target is to admit ten students every year to a combined programme (MD/PhD, Clinical research trainee [Agiko]) in each UMC. The combined annual costs for all eight UMCs would therefore be just over 14 million euro.

Advanced courses

Because of their existing knowledge and expertise the UMCs play an important role in the advanced courses for training as medical specialists, general practitioners, public health specialists, elderly care physicians or physicians for people with intellectual disability. Professors in clinical specialisms are often also teachers and usually play a prominent role in establishing training requirements and monitoring quality and innovation in these specialist courses. In view of the special type of patient admitted to UMCs, trainee specialists (AIOS) will also follow part of their training in a general hospital and/or a centre catering for a particular category of patient. The UMCs organise the advanced courses for family doctors and specialists in public health care, but they are of course provided in external practices and institutions. The idea of a training continuum ('lifelong learning') has given rise to a growing cohesion between the training as medical school graduate, the advanced courses and the post-academic education. Each of these forms of education profits from educational developments such as skills labs, cross-discipline education and competence-oriented curricula.

Efforts have been made for years to integrate advanced courses and scientific research, for example in the Agiko construction, where the specialist training is combined with a doctoral project. Such constructions promote the interaction between research and practice since they train professionals with substantially more skills in the area of scientific research and researchers with a good awareness of clinical practice. One point that requires attention in this context is the financing from the Training Fund. The rigid rules for this fund currently prevent a combination of advanced training and scientific research.

Professionalisation of the training

A good researcher, clinician or general practitioner is not necessarily also a good teacher. A national working group recently produced a list of the competences that teachers and trainers ought to possess. This marks an important first step towards improved quality assurance. Efforts are already underway at various levels to improve the didactic qualities and other competences of teachers and trainers. With their wide range of training facilities, the UMCs play a pioneering role in the professionalisation of teachers and trainers in their education and training regions. If the decision is made to raise the numerus fixus, an even greater effort will be required to train sufficient teachers to maintain the quality of the education.

Other courses: scope for local ambitions

In contrast to medical training, in which the differences between programmes are relatively smaller, there is a wide diversity in the other medicine-related courses provided in the UMCs and/or other faculties in the same university. These are often courses that train researchers or policy makers and are closely related to the local profile of the UMC, the university and sometimes even institutions of higher professional education (HBO). Accordingly, there is a wide variety of Bachelor's and Master's courses. Many places offer courses in biomedical sciences and/or health sciences. The UMCs and associated universities also offer courses in human movement sciences, dentistry, pharmaceutical sciences, medical information management, 'health and living' and medical natural sciences.

The dentistry programmes are currently reviewing their curriculum in connection with an extension of the duration of the course. The existing five-year course will be replaced with a six-year course: a three-year Bachelor's programme and a three-year Master's programme. The longer duration of the course will allow more time to prepare the graduates for an increasingly complex professional practice, important elements of which are the increasing importance of general medical knowledge, more complex dental problems and the shifting of tasks to and cooperation with other professionals. The longer duration of the course will also provide an opportunity to intensify the scientific education of the graduates and promote the development of 'evidence-based dentistry'.

The Master's courses are perhaps even more diverse. Various UMCs offer English-language courses that are provided in a European context in fields ranging from the neurosciences to oncology and from public health to molecular medicine. Many Master's courses are extensions of the institution's own Bachelor's courses and are naturally also open to students who have secured their Bachelor's degree elsewhere. However, Master's programmes are also offered for students with Bachelor's degrees in higher professional education.

Graduate schools

The *graduate schools* that have been established in all UMCs in recent years stimulate the education and training of PhD students as researchers. These *graduate schools* have brought more cohesion to these programmes. Through these programmes combining professional knowledge and methodology, for which certificates are awarded, PhD students are not only offered education of a guaranteed quality, but also the possibility of forming a social network. Systematic attention is devoted to the social and academic skills of the PhD students. There are differences of emphasis between the UMCs, depending on the programmes they offer besides medicine. The research Master's programmes in these other subjects, such as human movement sciences or biomedical sciences, are usually part of the graduate school. Nowhere are the regular Master's programmes in medicine and dentistry, for example, given in a *graduate school* context.

Accordingly, the eight UMCs focus their effort on promoting breadth and depth. In terms of 'breadth' the aim is to produce professionals with the necessary knowledge and skills and the correct attitudes to function well in the Dutch health care system; professionals with sufficient curiosity about new knowledge and skills and the capacity to reflect critically on their own attitude from time to time.

It is also very important to keep in mind individuals with special talents who can contribute to the progress of scientific research and clinical practice. After all, the quality of scientific research is ultimately determined by the talents of scientists.

5 | Working together on success

5 Working together on success

The eight UMCs are at the forefront of innovation in care and product development. The necessary innovation can only be achieved, however, with synergy and through cooperation with partners such as other research institutes, health care institutions and companies. There is cooperation all the way from the local level up to and including European and worldwide alliances. Naturally, successful cooperation depends on the powerful input of the UMCs themselves.

Good cooperation is always based on reciprocity. The Dutch UMCs have something to offer and therefore welcome partners for other institutions in the Netherlands and abroad. This cooperation enables them not only to maintain and strengthen their international competitive position, but also to offer outstanding education and high-class patient care and, through innovation in care and valorization, make a contribution to solving the major health care problems in the 21st century.

The CERN model

The domains of physics and technology provide numerous good examples of successful cooperation that yielded an exponential increase in the possibilities. The classic example is, of course, the cooperation in the field of particle physics. No country in Europe could have set up and maintained an organisation like CERN on its own. The investments that were made in CERN's physical infrastructure also led to a concentration of leading talent that is unique in the history of science.

A similar situation is currently emerging in the biomedical sciences, where challenges and technological possibilities are converging. The challenges take the form of major social issues. This is not just a question of science driven by curiosity, but research questions that are dictated by the day to day confrontation with actual health problems. Nevertheless, the UMCs would also like a 'CERN-like' approach in this context so that the necessary breakthroughs can be made by concentrating infrastructural facilities and talent. In this chapter we look at the various levels at which synergy exists, or could be further increased – from the local level to the larger partnerships.

Interaction between research and (top reference) care

The creation of the UMCs strengthened the synergy between scientific research and high-class patient care at local level. This interaction is so strong now that it is difficult to think of the two components independently of each other. Scientific research is stimulated by specific problems that occur in the clinic, by the availability of data and materials from patients and by the network of professional contacts of the clinicians. The close relationship with scientific research in turn enhances the quality of care for patients.

Partly because of the close-knit relationship with the scientific research, the UMCs can help patients who are unable to receive adequate professional care elsewhere. This is the top reference function, or last resort function, of the UMCs (see also the text box). Through their personal involvement with scientific research, the medical specialists in the UMCs have easier access to professional literature and to a network of colleagues in the Netherlands and abroad. Scientific research in the UMCs can ultimately lead to diagnostic or therapeutic interventions that can be applied more widely in health care in the Netherlands or elsewhere – or to the scientifically proven finding that a particular intervention makes no contribution to effective care.

The first step towards implementation is usually made in a UMC's immediate environment, in its partner hospitals and health care institutions (in the context of multi-centre studies, education, training, consultation, etc.). Networks and workplaces have also been established around the UMCs in primary health care and public health care in which knowledge and experiences are shared.

Multidisciplinary cooperation within and between research institutes

It is impossible to think of a medical discipline in which a single science can find an answer to every clinical problem. Input is always needed from different fundamental disciplines and from experts in the area of application. The relevant areas of science might be in the natural sciences or the social sciences. That fact provides opportunities for synergy in research and education in association with other faculties in the university itself or research institutions elsewhere.

Top reference: the UMC as ‘last resort’

A UMC distinguishes itself from other hospitals through the interaction between patient care and research and education. The concentration of expertise in the UMCs can provide added value for patients. This is particularly true for patients suffering from a rare complaint or an orphan disease, or from an unusual complication of a more common ailment. The care provided for patients who are referred to a UMC specifically because of its additional possibilities is known as top reference care. It is not always possible to say precisely what care falls into this category. For some complaints, such as various forms of cancer, the relevant professional groups have made agreements on which patients should be referred to a specialist centre. With other complaints, a combination of diseases (comorbidity), for example, may make the situation so complicated that reference to a UMC is useful. Patients are also regularly referred because treatment elsewhere has proved unsuccessful or has led to complications. In short, because top reference care focuses on those patients who cannot be adequately treated elsewhere, its boundaries shift depending on the possibilities of general hospitals. Technological changes, for example the development of new medicines or methods of treatment, could mean that in future patients who are now treated in a UMC will be able to receive optimal care in a general hospital.

A good example of the latter is the cooperation in the area of medical technology and tissue engineering between the UMCs, TNO and universities of technology. Advances in this field require cooperation between clinicians, biologists with knowledge of (stem) cells, engineers and chemists with expertise in biomaterials and bioreactors (instruments in which tissue can be 'built'/cultivated under controlled conditions). Initiatives by individual researchers have meanwhile led to structural cooperation between UMCs and universities of technology, for example in the Dutch Tissue Engineering Programme (DTPE), DutchFoRM and the leading institute BMM. A substantial SmartMix grant has also been awarded for research in this area.

An important element that demands attention in all these developments, and in the application of genomics and other groundbreaking technology in medicine, is the ethical and psychosocial aspects. Here too the UMCs do not need to possess all the expertise themselves, but can address these important issues through close cooperation with ethicists and social scientists.

Joint vision: NFU

The NFU was established in September 2004 as the successor to the Association of Academic Hospitals (VAZ). The following quote, which remains valid today, is taken from a positioning memorandum that was published at that time: 'The UMCs face the challenge of respecting the competitive element while at the same time preventing an irresponsible dilution of talent and resources. Anyone who surveys the research landscape will find that they have been reasonably successful. Every UMC has its own research profile and there are good and fruitful forms of cooperation between the leading groups in the UMCs. The cooperation with other faculties in the university and with groups outside it, including abroad, should also be mentioned in that context.'

Orphan diseases

One particular category of patient that will often require top reference care is those people with a very rare complaint (*orphan disease*). Roughly 8,000 patients in the Netherlands suffer from such a rare disease. The UMCs play an important role in providing care for these patients, often in close combination with scientific research into the causes of the disease. Many, but certainly not all, are hereditary complaints. The scientific research, as well as the diagnosis and possible treatment, generally calls for a multidisciplinary approach. The origin of some orphan diseases (there are 5,000 – 8,000 of them) provides evidence about the causes or course of more common diseases. The treatment of these rare diseases also sometimes provides leads for dealing with other diseases.

Patients with very rare diseases need to be concentrated in one or just a few centres so that the necessary knowledge and expertise can be consolidated. However, the researchers from different institutions will often have to cooperate to fit together the various pieces of the puzzle. If the number of patients is very small, cooperation at European or even global level is the only way of helping these patients. Even where treatment is not yet possible simply providing adequate information can already mean a lot to patients and their relatives.

A clearly expressed joint vision also facilitates cooperation with other partners, such as the collaboration with other health care institutions in the National Programme on Care for the Elderly (see text box) and with the business community. The UMCs recently adopted a common policy on valorisation in the memorandum *Naar een goede waarde* ['Creating value from research'] (12). Research institutes and the business sector also recently published a joint vision paper on the future of the life sciences (13).

Together with KNAW, NWO, VSNU, TNO and AcTI-NL, a strategy for investment in knowledge from the Economic Structure Enhancing Fund (FES) has been developed. Investment in knowledge is an important factor in this country's future economic success. Comparisons with other Western countries show that the Netherlands invests relatively little in the infrastructure for scientific research. The FES funds represent a positive exception in this regard, but their more or less unpredictable nature makes it difficult for individual institutions or consortia to base long-term policy on them.

The organisations concerned would therefore like the government to determine the amount to be invested in the 'technology and knowledge infrastructure' over a somewhat longer period. They also call for improvements in the process of submitting applications for projects. At present, they are handled via the various ministries. If consortia of research institutes and/or companies could submit applications directly to the relevant minister the procedure would be more transparent and improve the process of weighing up the applications. The organisations also call for better guarantees of the scientific or technological quality of applications. The system of assessment adopted by NWO and ZonMw does provide effective guarantees that projects are selected on the basis of quality.

Centres of expertise

The UMCs endeavour to meet the needs of patients, including their need for information, particularly concerning disorders that can be classed as falling within their top reference function. The NFU has taken a first step in this direction by building a website devoted to the top reference functions of the UMCs. The site contains an average of four functions in each discipline for each UMC so that patients can see where the priorities lie in the top reference patient care. Some UMCs provide additional information about specific complaints on their own websites. More will be done in this regard in the coming period, particularly for orphan diseases. It must be clearer to patients and referring physicians (general practitioners and specialists) what specific expertise each of the eight UMCs has. That includes information about orphan diseases, but also the effects of disease on capacity for work or, for example, the presence of a clinical research programme devoted to a particular complaint. Patients can then be referred to these centres of expertise for a second opinion and treating physicians can secure information from them, and if necessary the UMC can take over the treatment.

Strong within Europe

Dutch medical researchers are well represented in the EU's Framework Programmes. Dutch researchers participate in 39% of the projects in the Fifth Framework Programme and in 45% of the projects in the Sixth Framework Programme dedicated to life sciences. This is due to the quality of medical research in the Netherlands and the close links between laboratories and clinics in the Dutch UMCs. The large investments in infrastructure, for instance in the field of genomics, also contribute to the strong position enjoyed by Dutch researchers in relation to their European counterparts. The Netherlands plays a prominent role in the EU's BBMRI biobanks initiative and Euro-BioImaging initiative. Dutch researchers will also be engaged in the *European Advanced Translational Research Infrastructure for Medicine (EATRIS)* programme dedicated to translational research.

European cooperation is also expanding in the field of clinical research, for example in the European Clinical Research Infrastructures Network (ECRIN), in which agreements are made, among other things, on the requirements for the performance of clinical research so that it complies with European and local legislation. Clinical research features prominently on the roadmap of the European Strategy Forum on Research Infrastructures (ESFRI), but not yet on the Dutch roadmap.

Cooperation in care for the elderly

The ageing of our society is probably the greatest challenge facing the health care system in the coming decades. With the number of young people who are able and willing to work in the health care sector shrinking, a lot of research will be required to meet the needs for care of the rapidly growing group of elderly. Some of that research will have to focus on the optimal organisation of care, with special attention for the frail elderly. The UMCs play a key role in the National Care of the Elderly Programme, which addresses this and other issues. This programme will hopefully produce some useful findings for the optimal design of care for the elderly in the coming years. However, a lot more information is also still needed about the process of ageing. How is it that some people remain healthy up to an advanced age while others suffer from various illnesses simultaneously? Which factors can be influenced and what is the best way of doing it? These and many other questions are being studied at the Institute for Healthy Ageing (TI-GO), an initiative of the UMCs, other research institutes and partners in the business community and public and semi-state sectors.

6 | UMCs' future vision: challenges and new answers

6 | UMCs' future vision: challenges and new answers

Patient care and the economy will start reaping the benefits of the biomedical revolution within the foreseeable future. In the coming decades, health research will also have to find answers for the consequences of ageing, the growing incidence of chronic diseases and other challenges. A new trend in biomedical science, the integration of knowledge from various disciplines, can provide new impulses for medicine. The UMCs want to play an active role in all these developments. That will require a robust infrastructure consisting, among other things, of biobanks, cohort studies and facilities for (molecular) imaging and translational research. The anticipated gains, scientific, medical and economic, will depend heavily on the willingness of everyone concerned to make long-term investments in this basic infrastructure.

There have been tremendous advances in biomedical science in the last century. They have already had a major impact on our everyday lives. The life expectancy of a child born in the Netherlands today is significantly longer than it was in 1900, having risen from 44 years in 1900 to around 80 in 2007. The quality of life of children, adults and the elderly has also improved significantly, thanks in part to the possibilities of medical care. The challenges facing us at the beginning of this century are therefore significantly different to those in the 20th century. Whereas the emphasis then was on mortality due to acute infectious diseases (often related to malnutrition), attention now is focused mainly on chronic complaints and nutritional diseases. The main priority then was child mortality, the main problem now is to find an adequate response to the problems of ageing. Whereas the emphasis in the 20th century was on reducing mortality due to disease, the emphasis now is on reducing the burden of disease and dealing with handicaps. The emphasis is now also more than ever on conserving and restoring our mental health (our 'mental capital' as the RGO puts it, see www.mentaalkapitaal.nl).

Partly thanks to the UMCs, the Netherlands is well equipped to transform these challenges of the 21st century into 'profit', both social and economic. This chapter discusses a number of likely developments that will demand permanent attention and investment by the UMCs themselves and by the government and private sector in the coming years. The UMCs first review the major challenges, before considering new scientific approaches and finally the infrastructural and other determinants of success.

Ageing, chronic complaints, mental health

The biggest challenge facing health care in the coming decades is undoubtedly the ageing of the population and the growth in the number of very old people. Many (chronic) diseases such as cancer and cardiovascular diseases occur mainly in the over-55s. A growing number of elderly people therefore means that the demand for care will increase. In view of the costs and people's desire to remain independent, we will have to find ways of providing care as close to the home as possible and with the fewest possible lengthy hospital admissions. This means that care will have to be organised differently, but also calls for specific know-how; in other words, scientific research and technological innovation.

The health problems of very old people are often complex. They may suffer from various physical complaints in combination with social, psychological and mental problems. Relatively little scientific research is being conducted into this group. Most clinical studies exclude patients over the age of 70 or so and do not cover people with multiple medical problems (comorbidity or multimorbidity). Scientists also need to study the process of ageing and the conditions for remaining healthy as one grows older. The care process itself needs to be examined more closely in view of the decline in the number of young people and the fact that fewer young people are interested in working in the caring professions.

The number of patients with chronic diseases (diabetes, cardiovascular diseases, COPD, various forms of cancer, arthrosis, rheumatic complaints etc.) is also growing, not only because of the ageing of the population but also due to other factors such as prosperity and lifestyle. Risk factors such as obesity and hypertension are also increasing in seriousness and frequency. These illnesses have a major impact on the quality of life of patients and their relatives. They also cause substantial direct and indirect costs (the costs of care, sickness and incapacity benefits and economic loss arising from absenteeism). There is often not enough known to effectively prevent these diseases, to limit the harm (secondary prevention) or to reverse the course of these diseases. Even if the primary illness can be cured, as in the case of cancer, the patient often suffers for years from tiredness and other complaints resulting from the disease and its treatment.

Another trend that is apparent in every age group is the increase in psychological and psychiatric problems. According to projections by the World Health Organisation, depression is set to become one of the leading health problems in the Western world in the coming years. Since depression and anxiety disorders often occur in the same individuals, the number suffering from the latter will also increase. Given the large numbers of patients and the consequences of these problems for quality of life and labour productivity, they are already having an impact, and will probably have a major impact, on society. Although no dramatic increase in psychoses is expected, these are frequently recurring and/or chronic syndromes, which often require lifelong care. Last but not least, the anticipated increase in the number of patients with Alzheimer's disease and other forms of dementia will have serious consequences for the care sector.

Integrative approaches: multidisciplinary, high-throughput, visual

The rapidly expanding technological possibilities are contributing to a number of scientific developments that will undoubtedly have an impact on medicine in the future. A characteristic feature of these new approaches is that they are aimed at integration. Whereas scientific developments in the past concentrated on exploring subjects in ever finer detail, now there is also a tendency to combine the knowledge from various disciplines into a larger picture. This is particularly important in medicine. It is the only way of solving complex problems relating to chronic diseases, which are after all complaints caused by the interaction of various genetic risk factors and environmental factors (18).

In the first place, this focus on integration means that problems are addressed from a multidisciplinary perspective. For example, in regenerative medicine engineers, cell biologists and medical specialists work together to find solutions for specific clinical problems (*see also text box on regenerative medicine*). This work brings together expertise in the field of biomaterials with expertise in the field of growth factors and stem cells as well as clinical knowledge and experience with the relevant syndrome, in the interests of current and future patients. There is cooperation of an entirely different sort between institutions in the National Care of the Elderly Programme, in which

the UMCs play a key role. In this programme they conduct research with other care sectors (from home care and general practitioners up to and including general hospitals) into ways of improving the organisation of care, with special attention for the frail elderly. The type of integration sought here is in fact to bring greater cohesion to the now often fragmented provision of care.

Characteristic of contemporary biomedical science is the application of high throughput technologies, for example in genomics (large numbers of genes), proteomics (large numbers of proteins) and in cell systems and tissue engineering, which allow medicines and other chemical substances to be quickly screened for their effectiveness and/or toxicity. These technologies allow hundreds or even thousands of tests to be carried out in the same time it used to take for a single experiment. This has changed the whole approach to science, in which the relationship between different variables can be identified. The buzz word used is systems biology, to distinguish this new approach from the usual, more reductionist approach in the life sciences. In medicine, where the vast majority of diseases are caused by complex networks of risk factors, such an approach is essential (18).

The technical possibilities for visualisation of life processes have also made it possible to reach a new level of understanding and insight. Imaging technologies have improved enormously in recent decades so that biological processes can now be displayed at every level from that of individual macromolecules up to organs and complete organisms. The added value, the rapid progress, comes from bringing together insights from various disciplines in a coherent manner. The translational research is also integrative to a certain extent: it bridges the gap between the laboratory and the clinic, between fundamental research and patient care.

Infrastructure as a precondition

An essential precondition for these trends in biomedical science is a robust infrastructure. The government has also devoted a lot of attention to this subject in recent decades. Partly thanks to the Netherlands Genomics Initiative (NGI), the Netherlands possess a sound infrastructure for genomics, proteomics, metabolomics and related systems-biology approaches. The initiatives described below in the area of biobanks and cohort studies also

came about thanks to investments by the government. Looking to the future, the main concern relates to the preservation of these facilities. The UMCs have themselves invested in facilities for translational research, sometimes in collaboration with companies. ICT constitutes a bottleneck that has become increasingly apparent in recent years, not only as regards capacity in terms of data storage and computing power, but also expertise in bioinformatics. The trends towards integrative approaches (systems biology, omics) outlined above impose particularly high demands on people and equipment in the field of information science. Specific investments are therefore urgently needed in this area. As called for in the vision document Partners in the Polder (13, see also chapter 6, Technology), this calls for a clear future vision with commitments for the longer term and a willingness to invest in the latest innovative technologies.

BBMRI, String of Pearls Initiative, LifeLines and the return on biobanks and cohorts

In 2007, the NFU launched the String of Pearls Initiative, a special project relating to biobanks. This project is a unique collaborative effort by the eight UMCs. Following a standardised procedure, the UMCs collect clinical data and biomaterials from all of their patients with one of the eight syndromes being studied (the 'pearls': cerebrovascular accident (CVA, stroke), diabetes mellitus, inherited bowel cancer, inflammatory bowel disease (Crohn disease and colitis ulcerosa), leukemia, neurodegenerative diseases (e.g. Alzheimer's), renal failure and rheumatoid arthritis/arthrosis). This project provides unique opportunities for research into these disorders, improvements in patient care and the development of new products. Each UMC is the project leader for one of the eight selected 'pearls'. As soon as the infrastructure is working the number of 'pearls' will be increased.

With the project the Netherlands has assumed a leading position in the field of biobanks. With the involvement of many different researchers and all of the UMCs in the project, clear agreements have had to be made on how data will be collected so that they can be shared. There were few examples of multi-centre biobanks like the String of Pearls Initiative in the world. A lot of pioneering work has been carried out in relation to the storage of materials, and in particular data. The String of Pearls Initiative has meanwhile produced

so much expertise that the approach is being adopted by others. Naturally, the entire project observes the utmost care with respect to the privacy and the consent of the patients, and possibly healthy individuals, whose materials and data are stored.

By extension to the String of Pearls Initiative, there is the European initiative regarding biobanks, the Biological and Biomolecular Resources Research Infrastructure (BBMRI). The preparatory phase started in 2008, with the Netherlands as one of the leading partners. The aim is to create a pan-European distributed infrastructure that provides conditioned access to new and existing biobanks. The Dutch consortium (BBMRI-NL) consists of the eight university medical centres, the Dutch Cancer Institute, the String of Pearls Initiative, the National Institute for Health and the Environment (RIVM) and the Vrije Universiteit in Amsterdam. BBMRI-NL is financed from a special budget for large-scale research facilities that the NWO has received from the Ministry of Education, Culture and Science.

The Netherlands' position in the field of biobanks will be further expanded and strengthened with the recent grant awarded from the FES funds for the LifeLines project, an initiative of the UMC Groningen that is now supported by all the UMCs. In this study, sick and healthy participants from three generations will be followed for at least 30 years to identify the factors that are relevant for the cause and progress of chronic diseases. LifeLines started in 2006 and more than 160,000 people will participate in the coming decades. This group will be large enough to draw far-reaching conclusions about the influence of genetic factors, lifestyle and environmental factors on the cause and progress of chronic diseases. The new subsidy from the FES funds will be used to establish a biobank with materials from all the participants. These materials will provide an additional source of information about genetic and environmental influences and to help in the early identification of diseases.

Several major cohort studies have also started in mental health care in the last few years with subsidies from ZonMw's *GeestKracht* programme: NESDA (devoted to anxiety, depression and the relationship between these syndromes), GROUP (devoted to psychoses), Trails (young people) and Generation R (children from birth). In these cohort studies blood has been

taken from the participants for screening DNA research (Genome Wide Assays, GWA) with which the relationship between genes and the existence of psychiatric disorders can be investigated. In the GROUP study, brain scans have also been performed on many patients, family members and members of a control group. Partly thanks to GROUP, the UMCs in Utrecht and Maastricht have received a large EU subsidy for further research into psychotic disorders.

The return on biobanks and cohorts will grow strongly over time. Up to now, most energy has been devoted to setting up the banks and cohorts. A start has also been made with analysing the baseline data.

During the follow-up period the effects will appear over time. Since most biobanks perform research into chronic complaints, it is precisely this longer-term perspective that is of the greatest scientific and clinical value. Such a facility also derives its value from the large numbers; the more materials and data from patients they contain, the more robust the scientific conclusions that can be drawn from the analysis. Over time the analytical techniques will also be improved, upgraded and refined so that more information can be derived from the same materials.

This all means that biobanks and cohorts require a long term commitment in financial and staffing terms. Structural financing is needed to maintain the infrastructure. Ad hoc financing can be secured for each specific study. We are therefore calling for structural financing for at least 10 years for BBMRI, and the associated biobanks, such as the String of Pearls Initiative, LifeLines and the cohort studies in mental care to ensure that they can continue.

Bio-imaging: a new look at molecules

Technological developments in the field of electron microscopy, fluorescent microscopy and other imaging technologies allow molecules to be accurately located and studied. By using different technologies the disadvantages of a particular approach can often be compensated to produce an increasingly complete picture.

This is fascinating for fundamental researchers who want to know how life processes occur in health and illness. Even more importantly, these discoveries increasingly lead to new clinical applications, both in the diagnosis and the treatment of diseases. Projects like the String of Pearls Initiative and LifeLines help to show which molecules can serve as biomarkers for early detection of diseases or of people with a greatly increased risk of disease. This creates opportunities for primary and secondary prevention. Given the great importance of these developments and the possibilities in the Netherlands in this field, the NFU has already decided to invest 120,000 euro to support an application on behalf of the Dutch section of the Euro-Bioimaging project. However, to attract sufficient talented people and set up and maintain a robust infrastructure, structural financing is also needed here.

Obesity and metabolic syndrome

A subject that will demand a lot of attention in the coming years is obesity. The NFU and the Ministry of Health, Welfare and Science jointly published a brochure on this subject at the seminar *Beïnvloeding van leefstijlen: zijn er grenzen aan de bestrijding van overgewicht?* ['Influencing lifestyles: are there limits to the fight against obesity?'] (19) in 2007. The most important conclusion of that meeting was that with the current state of the art in medical science the possibilities of permanently reducing existing obesity are limited. Although scientific knowledge about the mechanisms that cause obesity is growing, experts are not optimistic about finding new ways of treating it in the short term. The promising medicine rimonabant has, for example, been taken off the market because of its serious psychological side-effects. New routes to effective treatments can only be found with an integrated approach, from systems biology to clinic. Obesity can be prevented, but that calls for coherent measures at national and local level. More is known about this subject abroad, but even then additional knowledge from a public health perspective is needed for its application in a Dutch setting. The Academic Collaborative Centres for Public Health, in which the UMCs participate, will contribute to this.

A significant number of people with (serious) obesity suffer from so-called metabolic syndrome, features of which are a high body weight, a reduced effect of the hormone insulin and a greatly increased risk of cardiovascular diseases. Since many of these patients will later develop diabetes mellitus type 2, metabolic syndrome is also regarded as a precursor of diabetes. There is a worldwide epidemic of obesity and metabolic syndrome, with potentially enormous consequences for public health in the coming decades. Whereas the ageing boom is inevitable, and will itself pose sufficient challenges for health care and society, it might be possible to curb this 'obesity wave' somewhat. But that will require knowledge of facets ranging from the fundamental biology of lipid metabolism and regulation up to and including the determinants of eating behaviour and the influence of social class, ethnicity and work.

People and equipment: innovation with sequencers, grid computing

Some specific areas of biomedical research are highly technology-driven. Accordingly, researchers must be able to invest in equipment to keep pace with the international competition and so remain interesting partners for their counterparts in other countries. One such area is the field of molecular biology. Whereas a lot of innovation in the last few years has been due mainly to micro-arrays ('DNA-chips'), the emphasis now is increasingly on the new generation of sequencers. These are instruments that can determine the genetic information in large parts of the DNA of an organism, or even a complete genome, in a fraction of the time it used to take. These instruments are expensive to buy and use but they are essential for innovative research in this competitive field. Technology is not just an essential ingredient for success in genomics, but also in other '-omics', such as proteomics and metabolomics. The importance of mass spectrometry to proteomics and metabolomics is a case in point.

First and foremost, these instruments yield an overwhelming volume of data. The next bottleneck is therefore the availability of computing power and knowledge in the field of ICT and bioinformatics. Bioinformatics scientists are needed to ask the right questions and so retrieve the most important relevant information from an ocean of data. ICT experts can find creative solutions for making the best use of the available computing power. One example is *grid computing*: the distribution of a complex computing task over a large number of computers to create a virtual supercomputer. One could even use the frequent occasions that a computer processor is relatively idle.

Translational research: bridging the gap between lab and healthcare

Despite the successes of translational research there is still a gap between fundamental science and clinical application. This is inherent to the practice of science itself but can only be resolved by looking more widely into possibilities for financing. The problem is that translational research, which is the essential translation of fundamental research (*proof of principle*) to clinical practice, produces little in scientific terms. For example, anyone who is able to cause cancer cells to disappear in a mouse by introducing a particular gene into some of the cancerous cells can count on a good article in a prestigious journal. But the person who then formulates procedures and quality criteria for introducing that gene into cancerous cells in humans under strictly controlled conditions has far fewer opportunities to publish the results, and almost none at all in the most prominent journals. Accordingly, these essential efforts are relatively insignificant when measured by the number of publications and citations, in short by the usual measures of quality for scientific research. This means that no external subsidies can be secured for this relatively expensive research – at least not if the grantor applies strictly scientific criteria.

In the past most translational research was performed by the research and development departments of pharmaceutical companies. But the new forms of therapy that are now being developed in the laboratory often first have to be applied in a high-tech setting, closely connected to high-quality patient care. Materials from the patients themselves are sometimes needed. Stem cells, gene therapy, advanced biomaterials and combinations of these ingredients are therefore essential, in contrast to a new medicine that can be distributed around the world in blister strips after careful testing. The research may in second instance lead to medicines in the usual sense, but the translational research must first be carried out within walking distance of the clinic where patients are being treated.

Various UMCs have established facilities, on their own or in association with companies, to produce biological materials under Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) conditions. However, these important facilities constantly require new investment to keep the equipment

up-to-date. Highly skilled personnel are also needed to operate the facility. Apart from the financing of the infrastructure, external funds are of course also needed to carry out translational projects.

The UMCs have repeatedly urged various bodies to expand the possibilities for the financing of translational projects. Their calls have led, among other things, to slightly greater possibilities from the health charities. Translational research in the field of molecular diagnostics, particularly for cancer, can be financed in the Center for Translational Molecular Medicine (CTMM), while for medicines the Top Institute Pharma might be an option. Otherwise, there are few if any possibilities for external financing of translational research. ZonMw has started a small pilot programme that is extremely popular among researchers. Unfortunately, its very popularity means that the chance of applications being granted in this programme are even smaller than in other ZonMw programmes. It would therefore be very welcome if ZonMw's initiative was rewarded with a contract from the NWO and/or the Ministry of Health, Welfare and Science or Economic Affairs. A careful assessment of the applications will make it clear that investing in translational research generates specific results for patients with (rare) serious disorders as well as for the Dutch economy. Without such an impulse too few important medical-scientific discoveries will find their way to the clinic and the market. The 'innovation paradox', the discrepancy between scientific quality and economic/clinical valorisation, will then remain.

Clinical research: the basis for sensible innovation in care

Clinical research is the crucial last step in innovation; what started in the laboratory and reached maturity in the translational GMP facility must ultimately prove to be better than existing care in a clinical study. Partly thanks to the creation of the UMCs, the Netherlands now occupies a prominent position in global clinical research. Clinical studies form the basis of rational medical treatment: *evidence based medicine*. Only a carefully designed clinical study, preferably involving the category of patients for whom a treatment or diagnostic intervention is indicated, can show whether it really contributes to better care. Clinical research can also be used to evaluate the effectiveness of a new intervention (for example in the ZonMw's Health Care Efficiency research programme 'DoelmatigheidsOnderzoek').

Regenerative medicine: recovery of tissues and organs

Our tissues and organs are constantly impaired by ageing and disease. This diminishes the quality of life of a growing number of people. Their cartilage degenerates (arthrosis) or their heart muscle no longer functions properly (heart failure), their lungs lose elasticity (COPD), vital structures in the central nervous system break down (neurodegenerative complaints including Alzheimer's disease). Or large quantities of healthy tissue are removed, for example because of a disease like cancer, with the ensuing cosmetic and functional consequences.

Up to now there has been almost no remedy for such decay. The research that has been performed in recent years, often in cooperation between UMCs and universities of technology, offers prospects for recovery. A new piece of tissue or even an entirely new organ can sometimes be cultivated under laboratory conditions (tissue engineering). Biomaterials, with or without growth factors and stem cells, can also be introduced into the body itself and generate the desired recovery. Studies are underway into which combinations of these components (stem cells, biomaterials, growth factors) and procedures (inside and outside the patient's body) would represent the best approach for the various disorders. Although a recent study by the KNAW (20) said that a lot more fundamental research is needed and we have to beware of expecting too much, these efforts will almost certainly lead to useful clinical applications in the coming years. The UMCs would like to gear their strategy to this.

The growing cooperation with the three universities of technology will also continue in other fields, so that the UMCs will continue to be closely involved in any medical applications of innovations in areas such as nanotechnology (for example *'labs on a chip'*) and robotics.

With these and other innovative developments it is very important to engage in a dialogue with the public and to keep in mind the ethical dimension. Some of the issues are of a general medical-ethical nature, which are more prominent in regenerative medicine. However, it is useful to actively discuss the ethical aspects of such a potentially important new technology with all the interested parties (20, 21).

The NFU's principal ambition in the field of clinical research is to maintain the current high standard. The most serious threat in this respect is the excessive regulation in some areas. The NFU naturally agrees that a very high degree of care must be shown towards patients and test persons, but the current rules and the associated administrative burden could put a stop to important research. This will be at the expense of the necessary progress in care and is therefore certainly not in the interests of Dutch patients. Extensive talks are being held on this subject with relevant organisations.

With their clinical research the Dutch centres contribute to the worldwide evidence and hence to the quality of care. Partly at the initiative of the NFU, the national cooperation will be further intensified. There can then also be cooperation at international level, for example in ECRIN.

The impact starts at local level however. Active commitment to clinical research make the clinics themselves more open to the results of research conducted elsewhere – and critical enough to distinguish the genuinely innovative research from the 'me, too' studies. It is also an advantage for the training of medical specialists if a department conducts top-class scientific research. Many clinical studies are performed in association with larger general hospitals. This makes it possible to use less 'selective' patient populations for studies – since a UMC has mainly 'top reference' patients. An additional advantage is that formal and informal networks of specialists are formed in university and general centres so that new knowledge can be disseminated more easily. This is one of the ways that the UMCs can play an independent role in the process of innovation in care: by developing and testing new technologies that can then, if possible and necessary, be applied elsewhere.

References

References

1 *Ministry of Education and Science,* Taakverdeling en concentratie in het Wetenschappelijke Onderwijs' *['Allocation of tasks and concentration in university education']* (1982)

2 *Operatie Selectieve krimp en groei* ['Operation Selective contraction and growth'] (1987)

3 *Advisory Council for Science Policy,* 'Prioriteiten in het gezondheidsonderzoek' *['Priorities in health research']* (1983)

4 Ministry of Education and Science (OC&W), *Stimuleringsprogramma Gezondheidsonderzoek* ['Health Research Promotion Programme'] (1986)

5 *Evaluation of Health Research Promotion Programme (SGO),* (1998)

6 Royal Netherlands Academy of Arts and Sciences (KNAW), *Discipline report* (1994)

7 Royal Netherlands Academy of Arts and Sciences (KNAW) and the Association of Universities in the Netherlands (VSNU), *Discipline Report on (Bio)Medical and Health Sciences Research in the Netherlands* (1998)

8 Advisory Council on Health Research, *Advies Brede Analyse Gezondheidsonderzoek* ['Broad Analysis of Health Research'] (1995)

9 *Dutch Federation of University Medical Centres,* Wetenschap gewaardeerd *['Science valued'] NFU-08.2389,* (2008)

10 Netherlands Observatory of Science and Technology (NOWT), *Wetenschaps- en Technologie Indicatoren 2010,* [Science and Technology Indicators 2010], NFU-10.0967 (2010)

11 Advisory Council on Health Research (RGO), *Research that matters. Responsiveness of university medical centres to issues in public health and heath care,* RGO (2007)

12 *Dutch Federation of University Medical Centres,* Naar een goede waarde [Creating value from research] NFU-09.1018 (2009)

13 Life Sciences Health, *Partners in the polder* NFU-09.4491, (2009)

14 Elsevier/ResearchNed, *special issue Studeren* ['Studying'], (2009)

15 Urlings-Strop et al., Medical Education 2009; 43: 175 - 183

16 *Council for Public Health and Care,* Numerus Fixus Geneeskunde: Loslaten of vasthouden, ['The numerus Fixus for medicine: should it stay or should it go'] (2010)

17 Dutch Federation of University Medical Centres. *Framework for undergraduate medical education,* NFU-09.2168 (2009)

18 *Royal Netherlands Academy of Arts and Sciences,* Multifactoral diseases in the genomics era (2006)

19 Dutch Federation of University Medical Centres. *Beïnvloeding van leefstijlen: zijn er grenzen aan de bestrijding van overgewicht?,* ['Influencing lifestyles: are there limits to the fight against obesity'] (2008)

20 *Royal Netherlands Academy of Arts and Sciences*. Well underway. Opportunities for regenerative medicine in the Netherlands, (2009)

21 *Netherlands Study Centre for Technology Trends (STT),* Converging Technologies, innovations patterns and impacts on society (2006)

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