Health Scientists at Odense University

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Preface

This booklet contains a collection of lectures given at seminars marking the appointment of new professors to the Faculty of Health Sciences, Odense University.

Each professor is a specialist within a particular field of knowledge and research. When a professorial seminar is held, the professor invites a guest lecturer within her/his field of interest. The combination of the new professor presenting her/his own research and the invited lecturer describing the field of research from an international point of view is intended to provide a framework for understanding the research area in question.

The texts from the seminars are published for the benefit of Odense University staff as well as other interested persons.

Mogens Hørder
Dean
Faculty of Health Sciences

May 1998

The elderly patient in general practice

- research theme for general practice at Odense University

Professorial Seminar
Thursday, 8 February 1996

Jakob Kragstrup

Jakob Kragstrup

Adj. Professor, DMSC, general practitioner.

Jakob Kragstrup was born in 1951. He graduated from University of Copenhagen Medical School in 1977. He held various hospital positions for 6 years, including 17 months in Tanzania, Africa. Since 1991 he has been a general practitioner, working in practices in Odder and Odense.

Jakob Kragstrup was appointed Head of the new Research Unit of General Practice at Odense University in September 1993, and in 1995 he became adjunct professor of health services research. He has previously worked as an Associate Professor at the Royal Dental College in Aarhus and at the Department of General Practice at the University of Aarhus. He has published a large number of scientific articles, a PhD thesis about toxicology and his doctorate of science thesis was about metabolic bone diseases.

Today his main area of interest is elderly patients in general practice.

THE Danish author and philosopher Søren Kirkegaard has described one of the dangers related to inaugural lectures:

"The researcher immediately distracts with his details; now he is going to Australia, now to the moon, now down into an underground cave, now studying any asshole - in search of an intestinal worm; now he is going to use the telescope, now the microscope; who the hell gives a damn?!..."

The purpose of the professorship seminars at the Faculty of Health Sciences in Odense is not to distract with details. My task is, in 20 minutes, to outline the professional environment which I have helped build up in Odense. I have invited Professor Per Fugelli, Norway, to give the broader perspective on research in general practice in a 40 minute lecture. Per will be known to many of you: as the doctor who practised for several years on a Norwegian island in the far North, who became one of the Scandinavian pioneers in general practice research, and who today is professor at the Institute of Social Medicine at the University of Oslo.

The Research Unit of General Practice

The Research Unit of General Practice in Odense was started in late 1993 with me as head of department. Even though it is placed at the University, the Research Unit is an independent institution, the purpose of which is to carry out research in general practice. It is financed by a Research Foundation instituted by the Danish Organization of General Practitioners and the Association of County Councils in Denmark. The Foundation had previously initiated similar research units in Copenhagen and Århus. All three units are independent institutions with their own Board whose members come from the Organization of General Practitioners and the Danish Health Services. The research units all have the same main purposes: 1) to do research in general practice, and 2) to educate researchers in general practice.

Targets for Research

The Research Unit and the University Department of General Practice in Odense discussed common research themes right from the start. The general practitioner has maliciously been described as "jack of all trades - master of none". There is also a risk that general practice research

groups occupy themselves with a little of "everything" without really gathering knowledge about "anything". The expertise obtained in a project is then related to the single researcher and disappears from the research environment if the researcher moves.

It was clear from the beginning that elderly patients in general practice constituted a possible target group. The first target formulations also emphasized that we wanted to focus on the decision processes of patients and doctors and stressed that we have special interest in longitudinal studies (episodes of care) and in pharmacoepidemiological studies.

The first formulations had one problem: they were far too complex to be a focus for anyone. Now we say it more simply: we have chosen "the elderly patients in general practice" as our research area. This patient group is of growing importance and makes new demands on general practice. It has been of importance for our choice that research regarding the elderly is given high priority in several departments at the Faculty of Health Sciences. We are part of the Centre for Aging Research together with health economists, demographers, epidemiologists, physcial education researchers and psychiatrists.

The process of giving priority to research areas is an ongoing process, and it would probably be an illusion to believe that we can set a firm strategy lasting for many years. The very act of phrasing (and rephrasing) research targets has, however, proved fruitful.

Targets for Education of Researchers

Lately, newspapers have been concerned about the problems which the hospitals have in finding physicians. Some have indicated that this problem would not exist if it were not for the fact that 700 physicians were fiddling about with their research at the universities. However, general practice lacks research competence. Among the more than 3000 Danish general practitioners there are perhaps 20 with a scientific degree, and there is an increasing need for "project makers" who can produce research and quality development. The SOFIE-report which, among other things, evaluated our area indicated a need for at least 200 general practitioners with a research education.

We have made research education of general practitioners and young doctors aiming at general practice a main task. For this purpose we

would like to use the PhD study which combines a research project with courses in research methodology. When enrolling PhD students we appreciate it if their research project fits with our research profile and if the PhD student is a general practitioner or a young doctor training for general practice. We greatly need the support of the Faculty of Health Sciences for this task.

Five Large Research Projects

Today in February 1996 we are working on five large research projects:

1. Episode oriented studies among elderly patients
2. Polypharmacy among elderly patients
3. Factors affecting the acceptance of influenza vaccination among the elderly
4. The effect of medical audit and reference programmes
5. Consequence evaluation of medical tests

Time does not allow me to go through the projects in detail, but I would like to tell a little about all of them. We have several other projects, and the researchers working with these projects should not feel rejected. These five projects have been chosen because they involve present PhD studies and because they illustrate that we have been able to make use of existing expertise in the university environment and in the region.

Episode Oriented Studies

An episode of care comprises all contacts between doctor and patient in relation to a specific health problem. Episode oriented studies are based on the very soul of practice work: continuous doctor-patient relationship. To describe work in general practice from what happens in one single consultation would be the same as wanting to describe the contents of a hospitalization from the case notes from one single ward round. Probably, something happened both before and after. Time enters as a parameter for diagnostics, planning as well as treatment, and work in general practice should be described from records of all contacts about the health problem (the total episode). This may seem obvious, but episodes of care in general practice have hardly been described. Knowledge of work in general practice comes from cross-sectional evaluations based on single consultations.

Our episode oriented studies are carried out in cooperation with 50 general practitioners from several Danish counties. Data about all contacts from elderly patients is collected prospectively from computerised patient records. The studies

have received large funds from the Ministry of Health and the County of Funen. Two PhD projects are related to the episode oriented studies: a methodological study and a study focused on the economics of episodes of care. Henrik Schroll looks into the methodological problems. Are data valid? Which epidemiological variables can be used to describe episodes of care? Annette Houmand is using the data for studies of health economy. This is done in close collaboration with the health economists at the Faculty.

Polypharmacy

Polypharmacy is defined as simultaneous use of several drugs. Combinations of drugs may have unforeseen effects and if several drugs are prescribed it may become difficult for both patient and practitioner to avoid mistakes. The problem is most frequent among the elderly. General practitioner Lars Bjerrum is preparing an epidemiological analysis of the phenomenon. The Department of Clinical Pharmacology at the University has established a unique register containing all prescriptions from recent years which have been processed by the pharmacies of Funen. The register allows an anonymized identification of persons so that prescriptions for the same patients can be followed for a period of time. We see great possibilities in cooperating with the Department of Clinical Pharmacology - and are happy that we were included in the application which recently resulted in a large multi-annual fund from the Research Council.

Influenza Vaccinations

Influenza is the epidemic disease causing most deaths in Denmark. It has been estimated that approximately 2000 persons died during the latest large epidemic in 1993 (mostly elderly people). Part of the explanation is that only a fraction of the risk group is vaccinated. Jørgen Nexøe is studying factors of importance for elderly persons' choice of vaccination. The study includes a qualitative interview investigation of a small group of elderly as well as a large epidemiological investigation of factors affecting the decision about vaccination. Further, a controlled trial is carried out in order to measure the effects of postal invitations and user fee on influenza vaccination rates among the elderly. Some may be cynical enough to think that those who die in an influenza epidemic are "just old fogies" who have not got much of a future. The study shows, however, that there is good health economy in a more systematic invitation to the elderly offering vaccination free of charge.

Audit and Reference Programmes

Annelli Sandbæk is close to finishing a PhD project which concerns reference programmes and

medical audit as methods for influencing doctors. To some of you her conclusions may seem a bit depressing. Practice patterns of GPs are not easy to change. We need more research into this field. Quality assurance is given a lot of interest these years and money has been earmarked for this purpose in the latest agreement between Danish general practitioners and the National Health Service. However, we still do not know what the most effective methods are. At Odense University we have good opportunities to work in this field because of Audit Project Odense (APO). Based on self-registration among general practitioners, APO works with quality assurance and quality development. APO has existed for a number of years and is now part of the Research Unit.

Technology Assessment

New diagnostic technology tends to sneak in. When a drug is marketed, it has to document its value and safety through extensive testing, including randomised blind studies with patients. New diagnostic procedures, however, can be introduced just like that! It is not without problems, as new tests may imply a risk - in itself or by giving misleading answers. When, occasionally, the value of a test is measured, it takes place in a hospital department. Therefore, we hardly know anything about the usefulness of diagnostic investigations in general practice where patients and diagnostic probabilities are quite different. Merete Skamling's PhD study makes use of a a very pragmatic method for assessing the value of tests. Patients are randomized into two groups and the test is used in one of the groups but not the other. The test's consequences for the patient's health are used as outcome measure.

In relation to this project the Department of General Practice and the Research Unit are part of SCOPE - a group with members from 7 EU-countries (funded by Biomed 2). The purpose of the collaboration is to study the possible use of health outcome measures for elderly patients.

FUTURE

An increased contact to general practice in our region will be given main priority in the coming years. The contact is already there, among other things because I and some of the other researchers are working part time as general practitioners. Further, general practitioners contact us with research ideas and questions. But we also have a problem: If we look at a map of the south-west region and mark the number of contacts, the density decreases almost exponentially

with distance from Odense. We have had a few contacts from the Counties of Vejle, Ribe and Southern Jutland, but Lillebælt seems to be an obstacle. In an attempt to obtain contact with colleagues interested in research from all of the south-west region of Denmark, we hope to be able to use two channels: Audit Project Odense and a new research consultant arrangement. It should to be possible to do research outside the university counties. To us it is of major importance to be in contact with our "growth layer": general practitioners interested in research. It is my opinion that contact to the primary sector in the south-west Danish region will also be of great value to the Faculty of Health Sciences in Odense.

Finally

I am glad to have the opportunity to thank Odense University and the Faculty of Health Sciences for appointing me adjunct professor in "health services research with particular emphasis on the primary health services". Some time ago the Dean Mogens Hørder during a minor disagreement told me that the only connection between the Research Unit and the Faculty is a tenancy agreement. Luckily this is wrong. As a tenant I am very dissatisfied with our chaotic room situation, however, I am very happy with the cooperative spirit in which the Faculty meets us.

Search and Research in General Practice

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Per Fugelli was born in 1943. He graduated from the University of Oslo in 1968. He worked for three years as a general practitioner in an Arctic fishing community located 100 kilometers West of the Norwegian mainland. Later on, he worked for three years as a general practitioner in Norwegian Lapland.

In these communities he experienced the value of personal doctoring and the importance of knowing the patients' social and cultural context.

Later on he has tried, through research and teaching, to refine and communicate the humanistic potential in general practice.

He has worked as a professor of general practice at the University of Bergen and from 1992 he is professor of social medicine at the University of Oslo.

He has published 20 books and 300 articles of which 80 report original research.

His main research interest at present is social cultural shaping of peoples' concept of health and disease, including tolerance for suffering, coping with risk and expectations to the health care.

The creed

General practice is a mysterious amalgamation of science, art and religion (1-3). Here is my creed:

- I believe in personal doctoring. Continuous relationship with patients is a conditio sine qua non for general practice. I believe in Sir William Osler's aphorism: "It is much more important to know what sort of patient has a disease, than what sort of disease a patient has" (4).

- I believe in a specific GP competence comprising generalized clinical skills adapted to the clinical probabilities and risk management typical for the front line morbidity and low technology setting.

- I believe in the GP as a master of pragmatic medicine, that is making medicine doable in the human jungle. I believe in Osler's saying: "The man who translates the hieroglyphics of science to the plain language of healing, is certainly the more useful" (4).

These are the eternal values, the DNA-molecules, replicating the nature of general practice from generation to generation.

Where is the beef ?

One essential task for research is to discriminate hopes in heaven from facts on earth. In current general practice there is perhaps too much ideology, too little science, too big advertisement, too little real thing.

Some years ago I travelled in the USA. At that time there was a new firm that tried to squeeze McDonalds' classical hamburgers. All over the country, on TV, in journals, on posters, they launched an intensive advertising campaign with a tempting colour picture of their hamburger roll with green salad and red ketchup:

- One time the hamburger on the president's desk in The Oval Office
- One time the hamburger in the hand of Bruce Springsteen
- One time the hamburger floating in the air in front of the Niagara Falls

Soon the consumers were brainwashed by the picture of the new hamburger and it started to go downhill for McDonalds. But then McDonalds hit cruelly back by introducing The campaign of all times, based on a poster where one half reproduced the competing hamburger with much bread, much salad and much ketchup, and the other half showed an ordinary

McDonalds with some bread, some salad, some ketchup - and a lot of beef, and an arrow over to the competing hamburger with the question: "Where is the beef ?"

There has been too much creed, too little rationality, too many soft words, too few hard data, in short: Too much ketchup and too little beef in general practice.

We have been clever to promote a picture of the general practitioner as conveyor of specific competences and values. We have constructed a sustainable ideology and sculptured a clinical profile respected by the politicians and appreciated by the patients. We have been clever with big words and high thoughts. We have been mediocre when it comes to research and documentation that can base general practice in evidence (5). We must leave prophecy and advocacy and approach the very substance of general practice, weigh it milligram per milligram, measure it millimetre per millimetre, analyse one atom at the time in order to crystallize the heavy metal of our discipline.

We have entered a positive development. We now have departments for general practice as well as research units at the universities. We have national colleges for general practice with European and global umbrella organizations. We do have international scientific journals for general practice and family medicine. We do have national, Nordic, European and world-wide congresses. In spite of these promising signs, the research in general practice is retarded, compared to the volume and quality of research in the other great clinical specialities: Internal medicine and surgery. The scientific laziness of the general practitioners is dangerous for the future of the discipline. It is of limited use that each individual general practitioner develops specific knowledge and competence if we are unable to transform these personalized skills to common goods. The thoughts and knowledge, the how-to-do-it-experiences are nothing but a waste of potentials in a couple of synapsis as long as the competence is jailed into the cranium of the individual. The experience, the knowledge must out via hand and pen, down to paper. Only then it becomes an object for critical analysis, only then it becomes an object for teaching and learning. Only then we can ensure the quality in our discipline. Only then we are a discipline.

RESEARCH AREAS IN GENERAL PRACTICE

Three gold mines lay there waiting for curious GP-minds (6,7):

EPIDEMIOLOGICAL RESEARCH

Many GPs are in an epidemiologically privileged position as they work in geographically limited areas with a well defined and well known population. Those doctors have monopoly on the morbidity in their local area. Furthermore, they accumulate knowledge of local environment and culture: Climate, housing, working conditions, family structures, religion etc. This provides the GP with a uniqe opportunity to trace interactions between environment and disease.

William Pickles represents a classical example of a colleague who realized the research potential of the local doctor. With sharp senses and an open mind Pickles visited farmers who coughed in the hay season in Wensleydale and he felt that here was "something rotten". With patience and precision he wrote down who coughed where and when, and thereby produced pieces to a puzzle that finally revealed a new disease: Farmer's lung. Pickles himself calls his scientific activity for "research of note book and shoe leather".

CLINICAL RESEARCH

Clinical problems and clinical procedures in the front line of the health services represent the most challenging area for research in general practice. James MacKenzie (8), pioneered this field 70-80 years ago. We should be concerned and a little ashamed that few have followed in his footsteps. A positive exception may be Jakob Kragstrup and the research milieu in Odense, who have selected clinical history of diseases in primary care as their research priority. MacKenzie was general practitioner in England at a time when rheumatic fever with heart failure was common. At that time the diagnostic criteria were rude and without mercy: A suspicious murmur was a kind of lifetime sentence, commanding young people to stay indoors, preferably tied to the chair or the bed for the rest of their time. MacKenzie could not quite understand the reason for this. He knew his patients, followed them over time and observed that several youngsters with auscultatory heart failure after rheumatic fever did not comply with doctors' order, but went fishing, and even made love in the forest. Two of the disobedient young patients even got pregnant and had normal deliveries, which, according to the truth of the time, was a completely unscientific act. After these observations, MacKenzie in the following years meticulously put down information on all

his heart patients, the localization and character of auscultatory findings, the nature of the patients' ordinary life, what they managed of physical efforts, in whom and after how long heart failure developed. After 20-30 years he was able to draw conclusions from his search and research in general practice, and publish his innovative work: "Principles of diagnosis and treatment in heart affection"(8).

It holds true for clinical research as for epidemiological research: The research questions must derive from the very nature of general practice (6). In clinical research the following general practice characteristics ought to be exploited:

The unselected morbidity

The primary clinician is confronted with the totality of the peoples' morbidity. The general practitioner manages five thousand episodes of disease every year distributed over the whole spectrum of organ specialities and diagnostic groups.

Health problems stopping up in the first line

Many of these diseases do never show up in hospital. Consequently, the research contributing to the correct diagnostic elaboration and treatment of these conditions, can only take place in general practice. This holds true for many of the infections of everyday life, complaints from muscles and joints, nervous trouble and social stress in somatic disguise.

Clinical probabilities and decision making in first line

The predictive value of the sympton cough is different in a GP office in Odense, compared to in the department of lung diseases in Odense University Hospital. The probability for the symptom headache to relate to brain tumour is greater among the patients in a department of neurosurgery, compared to the common population on Fyn. Improved insight into clinical epidemiology in the setting of general practice will make it possible to readjust the diagnostic calculator from the rarities of the university clinic to the realities of primary health care. On this background it is applaudable that the research milieu in Odense has made clinical decision making in general practice a main interest of research.

The unfinished disease picture

The fourth research challenge in general practice follows from the GP working in the first line of health services. This means that the GP confronts many diseases in their unclear and fluc-

tuant status nascendi. The unfulfilled disease picture is a prevalent clinical challenge in general practice. Many of these may-be-diseases never develop to conditions in accordance with classical diagnosis. The research should enlighten the GP's wait and see and step by step diagnostic procedures vis-a-vis this manyfold of vague and transitory complaints and signs.

Personal doctoring

The diagnostic and therapeutic potential in the personal doctor-patient relationship should be scrutinized through research. Is continuity of care always an advantage? May continuity result in a kind of same-procedure-as-last-consultation attitude?

General practice as pragmatic medicine

Research can refine the most noble competence of the general practitioner: The talent for transforming theoretical knowledge to earthly action. In the colourful and strange play we call peoples' everyday life we, the doctors, often play minor roles. Out there in the jungle, many other demands and influences will dominate. Very often the wise general practitioner has to renounce textbook solutions and find practical compromises determined by what is possible for this human being on this Wednesday ?

HEALTH SERVICES RESEARCH

Health services research comprises analysis of structures, functions and interactions in the health care system. Important topics are consumption of health services, division of work and cooperation between different professions and levels in the health service, cost benefit studies, studies of help seeking behaviour and patient satisfaction. Danish general practitioners have, in rude estimate, approximately 25 million patient contacts every year. They perform or order 15 to 20 million laboratory tests, prescribe 8 - 10 million drugs, refer 1 million patients to specialists, demand 6 - 700 000 X-rays, admit 6 - 700 000 patients to hospital. There is an obvious need for more research into the anatomy and the physiology of the health service itself.

ORGANIZING RESEARCH IN GENERAL PRACTICE

The general practice research is in Denmark, as in other countries, in puberty, full of potency and possibilities, but also with uncertainty on own identity. General practice has been on the move upward the last 20-30 years and has achieved great political support and high professional self esteem. But from the research point of view, we still suffer from obvious weaknesses (5).

The research is spread over a vast register of topics and over the whole spectrum of methods. Jakob Kragstrup has stated: "The risk is that our research milieu engage a little with the whole, without collecting evidence on specifics". The GP researchers have been lonely riders, riding through their thesis, and then, too often, put their horse on the stable. After 20-30 years of research in general practice we look out on a huge landscape with a little building of knowledge here and a little building of knowledge there, there are few connections between them, few attempts to build high and penetrate deep.

There are logical reasons for the diversified nature of general practice research.

General practice is an applied discipline. The scene is contemporary society. The players are people and doctors in this very moment. The drama is suffering and illnesses related to current environmental, political and cultural strains. Consequently it becomes tempting for GP-researchers to jump on the bandwagons and steer the research towards popular here-and-now demands. The result may be a research policy without profile, continuity and sustainability.

Another reason for diversity in research is the pendulation between the jungle and the academy in general practice (9). The GP-academics try to serve two masters. They want to obtain credibility and esteem among their scientific colleagues at the Faculty of medicine. Sophisticated projects performed with subtle methods and published in highly reputed international journals are the golden currency in this world. But out in the jungle, this type of research may be rejected as irrelevant. The GP-researchers are eager to please the academic potentates, but at the same time, they are dedicated to the field, and want to contribute to the quality improvement among the general practitioners. Academic research and quality assurance are two different tasks. The GP-academics are torn between these two obligations. Few have the courage to make a definite choice. The result is heterogeneity in GP research.

Internationally there is a promising trend where some GP research milieus advance from the entrepreneurial phase into a more mature state characterized by penetration of a few, essential research questions (10-13).

THE END

The research milieu in Odense represents one of the pioneers trying to change research policy from "opportunity knocks" to solid structure. You have elaborated a research strategy:

- giving priority to a few well defined research questions
- favouring long-term research enabling you to construct knowledge word by word, project by project, year by year.
- stimulating the formation of research teams with members not only from the medical profession, but in addition demographs, economists and anthropologists.

This is a wise strategy that will contribute to shift the nucleus of general practice from creed to science. Good luck.

REFERENCES

1. Fugelli P. General practice in the megazone. Fam Pract 1997; 14: 12-6.
2. Heath I. The mystery of general practice. London: The Nuffield Provincial Hospitals Trust, 1995.
3. McWhinney IR. The importance of being different. Br J Gen Pract 1996; 46: 433-6.
4. Bean WB ed. Sir William Osler. Aphorisms from his bedside teachings and writings. Springfield: Charles C. Thomas Publisher, 1951.
5. Howie JGR. Addressing the credibility gap in general practice research: better theory; more feeling; less strategy. Br J Gen Pract 1996; 46: 479-81.
6. Sweeney R, Jones JG. The case of family practice and primary care research at the NIH. Am Fam Phys 1993; 47: 37-9.
7. Wright AF. Moving foreword on research. Br J Gen Pract 1991; 41: 178-9.
8. MacKenzie J. Principles of diagnosis and treatment in heart affection. Oxford University Press: London, 1926.
9. Jones R, Spencer J. Making changes? Audit and research in general practice. Br J Gen Pract 1993; 43: 359-60.
10. Almind G. Structures and strategies for general practice research in Denmark. Scand J Prim Health Care 1993, 11 Suppl 2: 8-9.

11. Jones R, Lamberts H. Research in general practice: Dutch problems, European solutions? Fam Pract 1994; 11: 330-2.
12. Mäkelä M. Strategies and structures for research in general practice in Finland. Scand J Prim Health Care 1993; 11 Suppl 2: 13-5.
13. Rogers J. Family medicine research: A matter of values and vision. Fam Med 1995; 27: 180-1.

Forensic Medicine in Odense

Professorial Seminar
Thursday, 6 February 1997

Jørgen Lange Thomsen

Jørgen L.Thomsen

Born 1944 in Copenhagen. Cand. med. University of Copenhagen, 1970. Specialist in Morbid Anatomy and Hospital Pathology, 1982. Diploma in Medical Jurisprudence (DMJ (Path)), London 1978. Fellow of the Royal College of Pathologists (FRCPath), Great Britain, 1994. Professor of Forensic Medicine, Odense University, April 1st, 1996.

Chairman of the Danish Society of Forensic Science since 1994. Main fields of research have been forensic aspects of alcoholism, Y-chromosome detection, and foetal growth. Since 1983 he has worked for various organizations with the aim of documenting human rights abuses.

UNIVERSITY professors have three functions: research, teaching and administration. Forensic medicine has the additional function of providing services for the police. We perform medico-legal autopsies, requested and paid by the judicial authorities. We cover Funen and the Southern Jutland, while the institute in Copenhagen takes care of Seeland and the southern islands and Århus covers the northern and mid parts of Jutland. The three institutes also provide forensic services to Greenland and the Faroe Islands.

The forensic profession looks upon its field in different ways. Some find the pathology aspects more interesting. Others put emphasis on the judicial/legal/ethical aspects and still others find the relations with society important together with the aim of preventing diseases/accidents/homicides/suicides. These different interests are reflected in the selection of research areas.

We have the great university privilege of being able to choose our research subjects, but our obligations to the judicial authorities do in a natural way influence our choice. We hold a "monopoly" in cases defined in the Danish "Coroners Act". In my opinion this fact gives us the obligation of sharing our experience with others with the purpose of prevention. To put it briefly: When we see things go wrong - we report it - and it should never happen again. I only need to mention fatalities in the work place, occupational diseases, road traffic accidents, drug abuse, suicides, etc.

I have chosen two subjects for my presentation:

Research in alcoholism.

Social aspects reflected in the documentation of human rights abuses.

Research in alcoholism

The intake of alcohol among the Danes has a pronounced impact on our work. About one third of our autopsies are in alcoholics. Alcohol intoxication is frequently the direct cause of death, and alcohol abuse may lead to death through the long term effect on the body. In homicide cases, suicides and accidents we often find high alcohol concentrations both in victims and perpetrators, significant for the fatal outcome.

Together with researchers in Copenhagen we have discovered alcoholic ketoacidosis as a likely cause of death in a number of alcoholics (1). The condition was first described in 1940 in USA (2), but was then forgotten for many years. The history is usually as follows: An alcoholic stops drinking after a binge - he also stops

Winsløwparken 17 with the Institute of Forensic Medicine

The author (right) teaching forensic medicine in Costa Rica together with US anthropologist Clyde Snow.

eating - he is living alone and is then found dead under circumstances giving no cause for suspicion of a crime. It is a well known entity in Forensic Medicine and the cause of death has until now been a mystery. The only abnormal finding has hitherto been fatty degeneration of the liver. The alcohol concentration is usually nil or low. We have found an accumulation of ketone bodies (D-betahydroxybutyric acid, acetoacetic acid and acetone) similar to the metabolic disturbances in diabetics. The condition is a result of an abnormal lipid metabolism. The previous alcohol intake has had an inhibitory effect on fatty acid oxidation, and a higher level of fatty acids are available. The starvation has furthermore a lipolytic effect. The alcoholic ketoacidosis is typically seen in abstinence periods with a low intake of food. The deceased have usually been living alone, and nobody therefore discovers that the alcoholic is gradually becoming unconscious because of the grave metabolic disturbances. The perspective is not only diagnostic. There is a preventive aspect, as we are able to recommend that alcoholics who stop drinking for shorter or longer periods should not be left alone and should be made to eat properly. In a prospective investigation in our institute we found 7% of alcoholics to have died from ketoacidosis. It means that there may be between 40 and 50 cases each year among the medico-legal autopsies in Denmark. As we only examine about 3% of all deaths, the number of fatalities is probably higher. We are now going deeper into analyses of fatty acids with the aim of achieving a better understanding of lipid metabolism and the mechanisms leading to the described type of death.

We are also interested in drug abuse. Together with The National Board of Health we examine drugs confiscated in the street by the police with the aim of achieveing a picture of the drug market, the changes in type, quantities and concentration. One perspective of the research in abuse is the multidisciplinary approach from professions investigating various aspects of drug- and alcohol abuse, such as epidemiology, pathology, toxicology, genetics, prevention, education. It is all done in the hope that increased knowledge will mean increased prevention.

The forensic profession has an interest and experience in clinical medicine, examining victims of rape, incest and other types of violence, as well as the perpetrators.

Social aspects reflected in the documentation of human rights abuses

The social aspects of forensic medicine: Cases of interest to society will cumulate in the institutes

of forensic medicine. The forensic profession has developed an ability for objective documentation. In the statements we do our best to express exactly what we know, how we deduct it, what we don't know, what we believe and the degree of certainty. Forensic statements always have a degree of flexibility as it is rare that we can utter anything with absolute certainty. This flexibility increases the credibility and forensic statements are usually respected as they stand. This impartial approach does not exclude a more humanistic attitude manifesting itself in the selection of projects. The profession has become more and more involved at an international level in the documentation of extrajudicial executions, torture etc. The medical profession has always, since Hippocrates, or even before that been occupied with the ethical obligations, but since the Nürnberg trials it has been obvious that these obligations are not inherent in every physician. There is a need for teaching, and since the Tokyo Declaration in 1975, many declarations and conventions relevant to the medical profession have come to light. The subject is now taught in the medical curricula.

The work on the rights of the individual creates the basis for qualitative as well as quantitative research.

The role of forensic medicine in the local as well as the global society will be of increasing significance and we feel that we are well prepared to meet future challenges.

References

1. Jørgen L.Thomsen, Søren Felby, Peter Theilade, Erik Nielsen. Alcoholic ketoacidosis as a cause of death in forensic cases. Forensic Sci Int, 75, 163-171, 1995.
2. E.S.Dillon, W.Wallace Dyer and L.S.Smelo. Ketone acidosis in nondiabetic adults. Med Clin North Am, 24, 1813-1822, 1940.

Remains of 7-year old girl, shot by the army and buried in the rainforest in the Philippines. Exhumed and examined for documentation purposes.

International aspects of Forensic Medicine

Derrick J. Pounder

Derrick J. Pounder

Professor

Professor Derrick J Pounder has been head of the Department of Forensic Medicine at the University of Dundee, Scotland since 1987. Born in Wales and educated in England, he trained in forensic pathology in the Republic of Ireland and South Australia before practising in Adelaide, South Australia and Edmonton, Canada. His main field of research has been in forensic toxicology while his service work has evolved a strong commitment to the documentation of human rights abuses. As founder member and past chairman of Physicians for Human Rights (UK), he acts as a consultant for a range of human rights agencies internationally.

THE social objectives of medico-legal systems together with the scientific base of forensic medicine represent universal elements. However, these global aspects differ from the international aspects of forensic medicine. International here means between nations and is concerned with the application of forensic medicine to legal issues which arise between nations. This has occurred in two broad areas.

The first is when a citizen of one country is injured or dies abroad, an event increasingly common because of the explosion in international travel. Here issues may arise in insurance and criminal law. Often concerns are raised over the quality of the forensic investigation in the foreign country. In Western Europe we are well served by university-based departments of forensic medicine practising their skills at a standard of excellence but this is not necessarily true elsewhere. Re-examination of these cases frequently discloses errors.

The second, and more important, area of international forensic medicine is in human rights law. Where there are allegations of torture or extrajudicial killing by state officials, these are a legitimate concern for the international community. The atrocities of the Second World War ended the legal view that state sovereignty allowed states to treat their own citizens as they wished, and the charter of the United Nations has firmly placed human rights within international law. Forensic medicine can and does play an important role in support of this international law.

Forensic medical skills are particularly relevant to the investigation of allegations of abuses against the right to life and the prohibition against torture. It is ironic that the first such investigation of a major human rights abuse was undertaken by the government of Nazi Germany. This was of the Katyn massacre in which thousands of Polish officers who were prisoners of war of the Soviet Union were executed by the NKVD (KGB). Later large numbers of forensic exhumations of concentration camp victims and other victims of Nazi atrocities were undertaken in support of the Nuremberg war crimes trials. Today a new international war crimes tribunal is investigating atrocities in ex-Yugoslavia and the Rwanda genocide. Again this tribunal has brought together forensic medical experts to undertake exhumations and autopsies on the victims with the intention of corroborating eye witness accounts, and identifying the dead.

In supporting international human rights law, forensic medicine has applied technological advances as well as conducting specific research

Professor Derrick Pounder at a teaching seminar in Nairobi, Kenya.

on the problems raised. Identification by DNA profiling has been particularly useful and exhumations in ex-Yugoslavia and Rwanda have included sampling for DNA testing. Torture is a special form of violence directed against the person and researchers have specifically addressed the problems of diagnosis. The Danish medical section of Amnesty International has researched the diagnosis of electrical torture injuries. The results have been incorporated into the protocol of the South African investigative authorities concerned to stamp out such abuses. In Turkey forensic colleagues used imaging techniques to demonstrate damage to the fibro-fatty cushion of the sole of the foot occurring as a result of falanga torture. A noticeable consequence was a dramatic fall in this type of torture in the geographic area where such medical documentation was possible.

Clinical forensic medicine has also played an important role in the documentation of torture and physical abuse where this has been alleged by asylum seekers. Increasing reliance is being placed upon forensic medical experts not only because of their diagnostic and interpretative skills but also because of their medico-legal reporting skills. The production of reports which are formulated in a way suitable for legal proceedings and which are impartial, fair and frank has proven invaluable in these politically sensitive cases.

International agencies are making use of forensic medicine in a more systematic way. The European Committee for the Prevention of Torture was formed some 10 years ago following the signing of the European Convention Against Torture by the members of the Council of Europe. It operates a preventative system of inspection of prisons, police stations and similar institutions and currently makes use of forensic medical experts from several countries. The European Commission of Human Rights which is an inquisitorial judicial body, immediately below the level of the European Court of Human Rights forms part of a redress mechanism. Where there are allegations of torture or extra-judicial killing the Commission has heard forensic medical evidence lead both by the complainants and by the responding government.

However, experts in forensic medicine are also "doctors at risk". Because of their position they may be drawn into human rights abuses or become victims of abuses. Most commonly forensic experts participate in human rights abuses by failing to document or failing to offer robust opinions in cases of abuse, torture or extra-judicial killing. Those committing abuses well recognise that without documentation or accurate opinion there can be no proof. As a result doctors working in forensic medicine may be coerced to breach their ethical duty of accuracy of observation, documentation and opinion. Such experts are themselves at risk of abuse if they refuse.

In all of these facets of international forensic medicine we see the discipline serving as an applied science to fulfil a social role. It is a science which seeks to disclose the truth in as much as it exposes the facts concerning the circumstances of injury and death. In doing so it provides a foundation on which to build preventative policies and justice. However, knowledge of the truth although a pre-requisite for justice is not a guarantee. Others in society, especially the legal profession, have an obligation to make full use of this disclosed truth.

Animals and models:
who cares?

Professorial Seminar
Friday, 28 November 1997

Merel Ritskes-Hoitinga

Biomedical Laboratory
Faculty of Health Sciences
Odense University

Prof.dr. J. Ritskes-Hoitinga

Professor Ritskes-Hoitinga graduated from The College of Veterinary Medicine, Utrecht University, The Netherlands, in 1986. In the years 1986-1987 she got her first experience in doing biomedical research in Japan, after having obtained a scholarship from the Japanese government. From 1987 she worked as a PhD student at the Department of Laboratory Animal Science, Utrecht University. In the same period a post-doctoral education as Animal Welfare Officer was attended. In 1992 she succesfully finished her PhD and Animal Welfare Officer training. From 1992-1996 she worked as an Animal Welfare Officer at the Unilever Research Laboratory, Vlaardingen, the Netherlands. During that period she was secretary and president of the Dutch Association for Laboratory Animal Science, and board member of the Felasa (Federation of European Laboratory Animal Science Associations). March 1996 she obtained a position as assistant professor at the Biomedical Laboratory, Odense University. From 1 July 1997 she was appointed as professor of Laboratory Animal Science and Comparative Medicine.

Definitions:

What is animal experimentation all about?

A Professorship in Laboratory Animal Science and Comparative Medicine at the Biomedical Laboratory at Odense University was established the 1st. of July 1997. What is Laboratory Animal Science? Laboratory Animal Science is a multi-disciplinary branch of science, contributing to the humane use and care of animals in biomedical research and the collection of informative, unbiased and reproducible data (van Zutphen, Baumans & Beynen 1993). In other words, in case laboratory animals are to be used, this should be done correctly, with concern for both the animal welfare as well as the collection of reliable scientific results. Fortunately these two things go together: when the animal welfare of animals in experiments is not secured, this may interfere with results, possibly making them unreliable. What does Comparative Medicine mean? Comparative Medicine is the study of the nature, cause and cure of abnormal structure and function in people, animals and plants for the eventual application, and benefit of, all living things (Bustad et al. 1976). When looking at the situation at Odense University, Comparative Medicine is focussing on the use of animal models. An animal model can be seen as a replacer of human beings. In other words, an animal model is used as an image of man, in order to investigate a physiological (a normal process) or pathological (an abnormal process, a disease) circumstance in question (Svendsen & Hau 1994).

Which types of animal models can be distinguished?

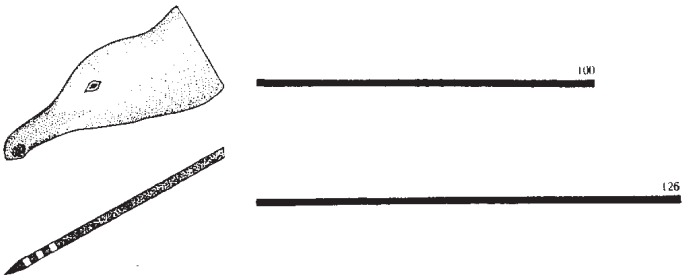
There are several ways of categorizing types of animal models (Svendsen & Hau 1994, Russell & Burch 1959). In the world famous book "The principles of humane experimental technique", written by Russell & Burch in 1959, the following categorization is presented. The types of animal models that can be distinguished are: 1. The fidelity model and 2. The discrimination model. A high fidelity model is defined as a model, in which all properties of the original are equally well/badly reproduced (Russell & Burch 1959). In a discrimination model, only one particular property of the original is reproduced (Russell & Burch 1959). In order to illustrate the meaning of these two categories, two illustrations of Japanese gardens are included. Gardens can be considered as a model of nature. Illustration 1 shows a Japanese garden, which can be considered as a high fidelity model from nature. The entire garden is modelled by human hands,

Illustration 1 - A japanese garden

Illustration 2 - A japanese garden

and all properties of nature are equally well reproduced. Illustration 2 is a Japanese garden, that can be called a discrimination model. The stones are used to symbolize water as well as mountains. Only one property of the original nature is reproduced. The calming effect of this discrimination model of nature can be larger than that of the high fidelity model, and even larger than nature itself. Therefore, we can call this a supermodel. Different models can provide us insight into which stimuli determine certain responses. This can be said about models of nature, as well as about models in biomedical research. Tinbergen & Perdeck (1950) performed an experiment, in which they used 2 models of a birds (seagull´s) head (Illustration 3). The top drawing illustrates the high fidelity model, as it resembles the seagull´s head in almost all aspects. The bottom one is the discrimination model, as it resembles one aspect of the head only, namely, the contrasting end of the beak. When these models were presented to young birds, waiting in the nest for their parents to come with food, the number of reactions to the top model was set at 100%. The number of reactions to the bottom model was 126%! So, the discrimination model gave a larger response than the high fidelity model. Therefore, the discrimination model can be called a supermodel. On a subjective basis, one often expects that a high fidelity model must be used in research, as this resembles the original in all aspects. However, the use of discrimination models, can provide us with more insight into which factors are important.

Illustration 3



Historical developments: diabetes mellitus treatment

In the following, an example is presented of how animal research has contributed to the progress of medical science. Type I diabetes mellitus in humans is a disease which is characterised by the absence of the hormone insulin, which leads to a rise of blood glucose levels. This is rapidly fatal, unless these humans are treated by insulin injections. It is estimated that about 30 million people worldwide need insulin therapy (1997). Looking back in history, already in 1889 it was discovered that pancreas removal in dogs caused diabetes symptoms in these animals.

Giving these pancreatised dogs a pancreas abstract injection did reduce blood sugar levels, but also caused fever due to impurities of the abstract (1909). In 1920 insulin was purified from beef pancreas: in order to detect the right fraction, blood sugar levels were measured each time a fraction was injected into rabbits. Two years later, purified insulin extracts were used successfully in dogs and human patients. As the treatment of diabetes mellitus by daily insulin injections does not cure the disease, the search for new therapies is continuing. One of the projects that is carried out at the Biomedical Laboratory, investigates the possibilities of transplanting insulin-producing cells into diabetic mice (thesis K.Yderstræde, 1997). If such transplantations could become succesful in mice, human trials must be carried out to evaluate whether this therapy will work in humans in a similar way. If yes, lifelong insulin injections for human patients with diabetes mellitus will no longer be necessary.

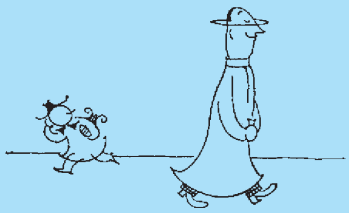
Choice of animal models

The first concern when using animal models for human diseases is, whether animal data can be extrapolated to the human situation. Or put it otherwise: are animal data applicable to humans? An animal looks like a human in many ways, that is why animals are used as models for humans. However, there are also differences. Therefore we can not apply data obtained from animal experiments to humans just like that. In order to obtain data from animal experiments that can be transferred to humans with the largest certainty, critical choices need to be made concerning which model(s) and which experimental conditions are selected. Because the choice of an animal model, the set of experimental conditions and the parameters measured, will (co-)determine the experimental outcome! The following example shows that a different model choice can lead to contrasting experimental results. Linoleic acid is a type of fatty acid used in margarin, in order to help to prevent the development of cardiovascular disease in humans. Animal experimental results indicated that dietary linoleic acid could stimulate the development of mammary cancer (Ip, 1985, 1993). From epidemiological studies no indications were obtained that dietary linoleic acid would stimulate breast cancer development in humans. Literature evaluations revealed that the influence of dietary linoleic acid level on mammary cancer development was dependent on the type of animal model used. A higher dietary linoleic acid concentration promoted mammary cancer development in animals only when chemicals were being used to

induce cancer. More dietary linoleic acid did not differentially influence mammary cancer development, when spontaneous tumour development at an older age was awaited. When mammary cancer was induced by infecting mice with a mammary tumour virus, cancer development could be delayed by a higher dietary linoleic acid concentration (Ritskes-Hoitinga 1996).

It is therefore very important that we put our research results into perspective. Illustration 4 shows a "grook" of Piet Hein, concerning a Pastor. The word "Pastor" can be replaced by scientist, as also scientists need to look beyond their "halo's". At times, scientists need to have a halo around their heads, in order to be able to focus on details. However, it must never be forgotten to relate research results to e.g. other people's results from animal experimentation as well as data from epidemiological studies and human trials.

Illustration 4



CIRCUMSCRIPTURE

As Pastor (scientist) X steps out of bed
he (she) slips a neat disguise on:
that halo round his (her) priestly
(scientific) head
is really his (her) horizon

Piet Hein 1966

Models and care

When surgery on larger animals is being performed, e.g. surgery in pigs and sheep, there is no doubt in people's minds that this needs to be done under sterile conditions. Sterility during surgery prevents infections. However, when surgery in smaller animals -especially rats and mice is done, then this is generally performed under non-sterile conditions. There is a worldwide believe that these rodents are "resistant to infections". Of course when laboratory animals are being used for surgery, they are healthy animals. This implies that they will not die from infections right away. However, doesn't non-sterile surgery interfere with our research results? Popp & Brennan (1981) compared sterile and non-sterile (aseptic) catheterization in rats. When rats are being catheterized, a small tube is inserted into the blood vessels, in order to collect "stress-free"

blood samples and/or do "stress-free" measurements and/or infuse substances into the circulation. "Stress-free" refers to the fact that it is not necessary to touch the animal. Touching will always evoke some kind of stress-response in the animal.

TABLE 1

	Catheterization (25 d)	
	aseptic surgery	sterile surgery
survival	3/6	6/6
infected catheter	5/6	0/6

Popp & Brennan 1981

Table 1 gives the result of their experiment. Sterile surgery led to a survival of all 6 rats in the group, whereas 50% of the rats that had undergone non-sterile surgery, died before the 25 days' period had ended. Sterile surgery prevented the occurrence of infected catheters. Five out of 6 animals developed an infected catheter after non-sterile surgery. An infected catheter is a catheter that becomes blocked, so it cannot be used any longer. This means that 5 out of 6 animals in the non-sterile group were lost for the experiment. In order to produce reliable scientific results, sterile surgery should also be performed in small rodents that are to recover after surgery. This example illustrates, that good care promotes good welfare and (more) reliable results.

PROJECTS AT THE BIOMEDICAL LABORATORY

At the Biomedical Laboratory, a wide range of biomedical research projects is carried out. Project topics vary from the production of antibodies to xenotransplantation. The species used range from (transgenic) mice to (mini)pigs and sheep. Research within the field of Laboratory Animal Science of the newly established professorship, focusses on the nutrition of the minipig and the short- and long-term welfare implications of food restriction. Comparative Medicine projects focus on the selection of colon cancer animal models that should aid in the development of finding better therapies for humans and a transgenic mouse model (Protein kinase transgenic mouse model) that may give us more insight into how cancer in general arises.

The minipig nutrition project focusses on establishing the nutrient requirements. Minipigs are increasingly used in scientific and toxicological research. Besides the microbiological and genetical standardization, the nutritional standardization is an important issue. The goals of this project are to establish a minipig diet that will prevent obesity, as well as nutrient deficiencies. This will aid in obtaining a better welfare and more reliable scientific results.

The goal of the colon cancer animal model project is to select (an) animal model(s) that is (are) most relevant for finding more succesful therapies for humans. First of all, available literature will be evaluated. Literature search is an important part of doing animal research, as this will prevent unnecessary duplication of animal experiments. In this same line of thinking it is essential to establish scientific contacts, so that a well-planned and well-defined research plan can be executed.

Who cares?

It is clear that our society cares for laboratory animals. There are legal guidelines that tell scientists what is allowed and what not. Each scientific protocol involving the use of laboratory animals must be evaluated and approved by a central committee in Danmark (Dyreforsøgstilsynet = Animal Experiments Inspectorate), before the experiment can start. The Inspectorate can also come on a site visit in order to judge whether procedures are executed in a correct manner. Personnel looking after experimental animals have a caring attitude towards animals, otherwise they can and should not work in this field. Professional care is provided by animal technicians and veterinarians, that have specialized in laboratory animals. Animal technicians attend a professional training of 3,5 years nowadays. Besides professional care, the "tender loving care" provided to the experimental animals is also very important, e.g. to guarantee a relatively "smooth" recovery after surgery. Odense University has shown their care for laboratory animals and animal models by establishing this professorship. The Biomedical Laboratory has already been teaching scientists to care for many years, as legally compulsary courses in Laboratory Animal Science are organized here. These courses provide scientists with the necessary information on laboratory animal science, before they are allowed to be responsible for doing animal experiments.

The newly established professorship is expected to add more service and support, and a higher

quality of scientific input, in addition to what the Biomedical Laboratory has excellently provided over the years. The high standard and quality of Laboratory Animal Science courses for scientists will be continued in order to guarantee a responsible use of laboratory animals in experiments.

References

Bustad, L.K., Gorham, J.R., Hegreberg, G.A. and Padgett, G.A. Comparative Medicine: Progress and prospects. Journal of the American Veterinary Medical Association, 169, 90-105, 1976.

Ip, C., Carter, C.A. and Ip, M.M. Requirement of essential fatty acid for mammary tumorigenesis in the rat. Cancer Research 45, 1997-2001, 1985.

Ip, C. Controversial issues of dietary fat and experimental mammary carcinogenesis. Preventive Medicine, 22, 728-737, 1993.

Popp, M.B. and Brennan, M.F. Long-term vascular access in the rat: importance of asepsis. American Journal of Physiology, 241, H606-612, 1981.

Ritskes-Hoitinga, J., Meijer, M., Meijer, G.W. and Weststrate, J.A. The influence of dietary linoleic acid on mammary tumour development in various animal models. Scandinavian Journal of Laboratory Animal Science, Suppl. 1, 23, 463-469, 1996.

Russell, W.M.S. and Burch, R.L. The Principles of Humane Experimental Technique. 1959.

Svendsen, P. and Hau, J. (eds.). Handbook of Laboratory Animal Science. CRC Press, 1994. Boca Raton, Ann Arbor.

Tinbergen, N. and Perdeck, A.C. On the stimulus Situation releasing the begging response in the newly hatched Herring Gull Chick. Behaviour, 3, 1-39, 1950.

Van Zutphen, L.F.M., Baumans, V. and Beynen, A.C. (eds.). Principles of Laboratory Animal Science. Elsevier Science Publishers, 1993. Amsterdam, London.

Yderstræde, K.B. Transplantation of insulin producing islet tissue. Evaluation of free and encapsulated syngeneic and xenogeneic islet transplants. Thesis, Odense University, 1997.

Laboratory Animal Science: A Contribution to Animal Welfare

Bert van Zutphen

Prof. dr. L.F.M. van Zutphen

After studying biology at the University of Utrecht, professor van Zutphen started his professional activities in 1968 as a teacher at the Vitus College in Bussum. He returned to Utrecht University in 1969 where he received his PhD degree in genetics (1974) and became an associate professor in animal husbandry and genetics at the Faculty of Veterinary Medicine until 1983. During the years 1976-1977 he worked for a period of eight months as NIH-Fogarty Fellow at the Jackson Laboratory in Bar Harbor (USA).

In 1983 he was appointed as professor and chairman of the Department of Laboratory Animal Science. He is the national coordinator for education in this field and director of the postgraduate training programme laboratory animal science. He is editor of eight handbooks/proceedings in the field of laboratory animal science, and is member of the editorial board of four international journals. He is author/co-author of more than a hundred research papers. He is serving as board member of various organizations on laboratory animal science, e.g. secretary of the Netherlands Federation of Laboratory Animal Science Association, vice-chairman of the governmental Central Animal Experimentation Committee and chairman of the national NWO Committee on Animal Alternatives.

Introduction

The performance of an animal experiment is not considered morally acceptable if there is a non-animal alternative available or if, according to the judgement of an ethics committee, the benefit does not outweigh the animal's suffering. For those experiments that have received approval of an ethics committee, every effort should be made to reduce the number of animals to the minimum necessary for drawing scientifically sound conclusions, and also to minimize suffering of the animals as much as possible. Russell and Burch (1959) wrote: *"Suppose, for a particular purpose, we cannot use replacing techniques. Suppose it is argued that we shall be using every device of theory and practice to reduce to a minimum the number of animals we have to employ. It is at that point refinement starts, and its object is simply to reduce to an absolute minimum the amount of distress imposed on those animals that are still used."*

The welfare of laboratory animals is jeopardized differently at different stages of their lives. Before the start of an experiment, the housing, breeding or transportation conditions may be inadequate. During the experiment the procedures and conditions may inflict pain and/or distress. Often these conditions not only have an adverse effect on the well-being of the animals, but also on the quality of the experimental results. Thus refinement often improves both the quality of experiments and the well-being of the animals. Two examples of research areas on refinement are presented. In addition, the importance of education and training for improving the quality of research and the welfare of the animals is pointed out here.

the use of preference tests for studying choice behaviour

Improvement of housing condition

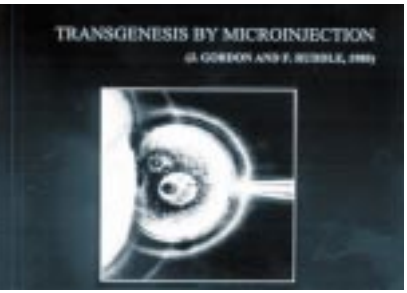
Mice and rats are generally housed in cages with either a solid floor with bedding material or with a grid floor. Dr. Vera Baumans at the Department of Laboratory Animal Science - Utrecht has initiated a programme using preference tests in combination with behavioural and physiological studies in order to improve housing conditions for laboratory animals. By applying this approach Blom (1993) has shown that grid floors are consistently avoided if there is an alternative of a solid floor with bedding. He also showed that bedding consisting of large fibrous particles was generally preferred to bedding consisting of relatively small particles. Van de Weerd (1996) has shown that when mice of two inbred strains (C57BL and BALB/c) are offered a choice between two similar standard cages, one with only bedding material and the other with

bedding material and nesting material (paper towels), the animals of both strains consistently chose the latter. Even a grid floor with additional nesting material was preferred over a solid floor with bedding only. Thus nesting material seems to be an essential and easy-to-use form of cage enrichment. A study on the influence of cage enrichment on intermale aggression is in progress.

Assessment of welfare problems in transgenic animals

Since the first successful microinjection of foreign DNA fragments into the mouse zygote in the early 1980s (Gordon et al. 1980), the quality of animal models in biomedical research has increased substantially. Applications of this microinjection technique, or of the later developed technique of homologous recombination in embryonic stem (ES) cells, has revolutionized the study of gene functions in development and diseases. Several of the traditional animal models have been replaced by more specific transgenic models. Also, in livestock production or in biopharming transgenic animals fulfill an increasingly important role. There is no doubt about the potential benefits of this technology.

Fig. 6



This, however, does not release us from the moral obligation to carefully consider the impact of transgenesis on the welfare of the animals. Most transgenic animals are produced through the microinjection technique. With this technique it is not possible to target the DNA construct to a specific locus on the chromosome. It is a random process and there is a risk of disturbing the balanced genotype due to insertional mutations which might have a negative influence on the functioning of the damaged gene(s) and thus on the health and well-being of the animal. Studies on the welfare of transgenic animals are still scarce. Studies on sheep and cattle have indicated that *in vitro* manipulations with the embryo may cause an increase of the gestation period, increase of the birth weight and perinatal loss of animals (Walker *et al.* 1996; Kruip and Den Daas 1997; Van Reenen and Blokhuis 1997). The mouse is by far the most frequently used animal species in transgenesis. So far there is no proof that the technique as such has a negative influence on the well-being of transgenic mice. To obtain more insight into this aspect, the (harmful) effects of the technique must be differentiated from the (harmful) effect of the expressed transgene. At our department a project has recently been started for studying the effect of genetic modification in several transgenic mouse experi-

ments. A test protocol was developed for the systematic observation of the animals and for collecting information that might be relevant for establishing the impact of transgenesis on the well-being of these animals (Van der Meer and Van Zutphen 1997). Within each of the transgenic experiments the physiological and ethological parameters that are included in the protocol are screened in four groups of animals, all derived from the same inbred strain. These groups are: transgenic animals, non-transgenic littermates, animals produced through microinjection with a non-functional construct of the gene and control animals (not microinjected). By this approach the effect of the technique can be differentiated from the effect caused by expression of the transgene. Besides testing whether the technique of transgenesis as such has an influence on the well-being of animals, this project also aims to evaluate the feasibility of the test protocol for monitoring welfare aspects. Based on a critical evaluation of the welfare parameters used in the test protocol a model protocol will be developed for the routine control of welfare problems in the production of (transgenic) mice.

Education and training

The implementation of results obtained in animal welfare research greatly depends on the competence of the persons who are involved in the design and performance of animal experiments. Competence must be based on education and training which should contribute to both attitude and skills. In many countries the legislative regulation of animal experimentation contains a section on the need of competence, but how competence must be achieved is not well specified in most of these laws. Both the Federation of Laboratory Animal Science Associations (FELASA, 1995) and the Council of Europe (CoE, 1994) have issued guidelines on education and training for each of the categories animal caretaker, technician, researcher and laboratory animal specialist. In the past some emphasis has been on the training of animal caretakers and technicians. This continues to be of utmost importance, but according to FELASA, priority should now be given to the education and training of persons responsible for directing animal experiments. These are usually the key persons who are responsible for the design of the study and the performance of the experimental procedures. If the Recommendations of FELASA or the Resolution of the Council of Europe are adopted, then every scientist who is responsible for the design and performance of

animal experiments must have completed a graduate study in one of the biomedical sciences (at the level of bachelor's or master's degree) and, in addition, must have taken an 80 hours course (or equivalent form of education) in laboratory animal science.

This course should include ethical aspects and legislation; biology and husbandry of laboratory animals; microbiology and diseases; design of animal experiments; anaesthesia, analgesia and experimental procedures; alternatives to animal use; and analysis of relevant scientific literature. In several European countries such a course has already been made compulsory by law. Laboratory animal scientists have taken the lead in organizing these courses.

Conclusions

Developments in the field of biomedical sciences, in particular in biotechnology, and the increased interest for the welfare of animals have changed the role of laboratory animal science. A major challenge for the laboratory animal scientist is to contribute to the new fields of animal science and, at the same time, act as an advocate of the animals and to seek for methods and procedures that can reduce their suffering or improve their well-being. The development of a high quality research programme and the organization of an education and training programme, both guided by the Three Rs approach of Russell and Burch, seem to be the appropriate tools for the implementation of the above mentioned objectives.

References

Blom, H.J.M. Evaluation of housing conditions for laboratory mice and rats. Thesis, Utrecht University, 1993.

Council of Europe Resolution on education and training of persons working with laboratory animals. Multilateral Consultation. Council of Europe. ICLAS News 4, 5-6, 1994.

FELASA Recommendations on the education and training of persons working with laboratory animals: Categories A and C. Report of the Federation of European Laboratory Animal Science Associations Working Group on Education. Laboratory Animals 29, 121-131, 1995.

Gordon, J.W., Scangor, G.A., Plotkin, D.J., Barbosa, J.A. and Ruddle, F.H. Genetic transformation of mouse embryos by micro injection of purified DNA. Proceedings of the National Academy of Sciences, USA. 77, 7380-7384, 1980.

Kruip, Th.A.M. and Den Daas, J.H.G. In vitro produced and cloned embryos: effects on pregnancy, parturition and offspring. Theriogenology 47, 43-52, 1997.

Russell, W.M.S. and Burch, R.L. The Principles of Humane Experimental Technique. London: Methuen. 1959.

Van de Weerd, H.A. Environmental enrichment for laboratory mice: preferences and consequences. Thesis, Utrecht University, 1996.

Van der Meer, M. and Van Zutphen, L.F.M. Use of transgenic animals and welfare implications In: L.F.M. van Zutphen and M. van der Meer (eds.) Welfare Aspects of Transgenic Animals. Heidelberg: Springer Verlag, pp. 78-89, 1997.

Walker, S.K.. Hartwich K.M. and Seamark, R.F. The production of unusually large offspring following embryo manipulations: concepts and challenges. Theriogenelogy 45, 111-120, 1996.

Van Reenen, C.G. and Blokhuis, H.J. Evaluation of welfare of transgenic farm animals; Lessons from a case study in cattle. Proceedings Int. Workshop Transgenic Animals and Food Production, Stockholm, May 22-24, 1997 (in press).