SYMPOSIUM REPORT:

Future Directions for Research in the Clinical Neurosciences: Policies, Strategy and Funding

The final plenary session of the 16th Canadian Congress of Neurological Sciences held in Calgary, Alberta in June 1981 consisted of a symposium to consider "Future Directions for Research in The Clinical Neurosciences". With the assistance of grants from the Alberta Heritage Foundation for Medical Research and The University of Calgary, a panel of speakers was assembled with representation from basic and clinical neuroscience and from government and privately sponsored funding agencies. Members of the panel included:-

Dr. Albert Aguayo — Professor of Neurology, McGill University: Head, Division of Neurology, Montreal General Hospital.

Dr. Donald Tower — Director Emeritus, National Institute of Neurological and Communicative Disorders and Stroke.

Dr. Louis Poirier — Directeur, Laboratoire de Neurobiologie, Laval University: President, Conseil de la Recherche en Santé du Québec.

Dr. Michael Graham — Vice-President, MS Society of Canada: Treasurer, International Federation of Multiple Sclerosis Societies.

Dr. Patrick McGeer — Professor of Neurological Sciences, University of British Columbia: Minister of Universities, Science, and Communication, British Columbia Provincial Government.

Dr. Keith Cooper — Vice-President (Research), University of Calgary.

Dr. John Desmedt — Director, Brain Research Institute, University of Brussels.

Dr. Joseph Martin — Professor and Chairman, Department of Neurology, Harvard University.

The main objectives of the symposium were to examine the current status of funding for neuroscience research with particular reference to clinical applications, and to discuss policies and mechanisms which will best promote the application of new knowledge emerging from the basic neurosciences to the solution of clinical problems affecting the human nervous system.

In a report of this type it is difficult to do justice to each of the speakers and to convey the full spirit of the discussion which took place. Nevertheless, believing that this is a topic of considerable interest to most of the readers of the Journal, we have attempted to highlight some of the main areas which were covered during the symposium.

CURRENT STATUS OF FUNDING FOR NEUROSCIENCE RESEARCH IN CANADA: DR. ALBERT AGUAYO

Dr. Aguayo reviewed the changes which have occurred in Medical Research Council funding over the six year period from 1974-1980. During this time the MRC budget has almost doubled. The total figure for 1981 is approximately $102 million. Neuroscience research appears to have kept pace with this increase, and in fact the MRC funds directed to the support of neuroscience projects are estimated to be more than double what they were in 1974.

In addition, non-government agencies make a major contribution. For example, funding by the Multiple Sclerosis Society of Canada represents about 10% of the total MRC budget for neuroscience research. The figure for the Muscular Dystrophy Association is approximately 19% of the MRC total.

Despite what may initially appear to be a fairly healthy situation, particularly in the light of the 22% increase in MRC funding in 1981, a closer examination of the breakdown in these figures raises some concerns. The total number of operating grants has increased by 13%. The value of the average award has increased some, but in most cases this has not been sufficient to keep pace with mounting inflation and the falling value of the Canadian dollar. The latter creates particular problems for purchasing research equipment, much of which must be obtained from outside Canada.

From the clinical research point of view it is interesting to note who is receiving these operating grants. While the number of grants has increased, there has been a slight decrease in the number of investigators holding M.D. degrees - 162 in 1974 compared to 158 in 1980. This implies that a larger proportion of the research is being done by non-clinical investigators. There has also been a decrease in the number of MRC fellowships awarded to graduates with an M.D. degree. Recent figures for MRC indicate that 30% hold M.D. degrees, 10% have both an M.D. and PhD, while 60% are PhDs.

Dr. Aguayo went on to review the structure and composition of an academic department. A successful clinical department must maintain a balance between its three major functions - patient care, clinical teaching, and research. These functions are interdependant and must all receive adequate support. The standards of patient care are improved by bringing together service, teaching, and research activities in one department.

To develop this type of clinical department three types of individuals are required: clinicians, physician-scientists, and "pure" scientists. Serious consideration should be given

to the recruitment of more PhD basic scientists to clinical departments. These individuals provide the stimulation, the expertise, and the critical approach which is required to ensure that high quality research is carried out. However, at the same time it is crucial that steps be taken to reverse the trend for a decreasing number of M.D.s to undertake post-doctoral research training leading to careers as physician-scientists. Mechanisms must be found to obtain more support for these individuals during their training period and subsequent establishment. Otherwise, we are going to be faced with a severe shortage of the type of person who is most urgently needed to provide the interface between basic and clinical neuroscience in an academic department.

THE ROLE OF GOVERNMENT AGENCIES IN THE FUNDING OF NEUROSCIENCE RESEARCH: DR. DONALD TOWER

Dr. Tower presented a detailed review on the current funding situation in the United States. Since 1950 approximately $75 billion of public and private funds have been spent on health care research and development. In 1950 the amount was about 0.06% of the Gross National Product (GNP); since 1974 it has been about 0.31% of the GNP. About 60% of this total expenditure and about 90% of the funds for basic research, come from the federal budget.

The U.S. budget for fiscal year 1982 can be summarized as follows. Out of a total of $695 billion, 10.5% or $73.4 billion is allocated for "Health". (This compares to 27.2% for defence and 34.6% for income security - two items which together account for 62% of the total 1982 budget). The major part of the "Health" budget goes to support things such as social security, medicare, etc. Only $7.4 billion (3.1% of the $228 billion total budget) can be considered as the discretionary or controlled expenditures. The National Institutes of Health (NIH) receive slightly over one half of this $7.4 billion or 0.54% of the total U.S. federal budget.

Most of the funds for neuroscience research supported by the U.S. Government come from the NIH, the Alcohol, Drug Abuse and Mental Health Administration (ADMHA), the National Science Foundation (NSF) plus smaller amounts from the Veterans Administration, the Department of Defence, and other agencies. The NIH budget for 1982 is proposed at $3.76 billion which represents an increase of 7.1% over fiscal year 1981. All other agencies in the health and related research area will experience drastic reductions.

The National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) has received particular visibility within the NIH 1982 budget by virtue of a $24 million increase of 9.5% over 1981. The NINCDS budget is to be allocated approximately as follows: 68.6% for research grants, 6.6% for research training (including career development awards), 3.8% for research contracts, 11.0% for intramural (on-campus) research, and 10.0% for central management and program direction. This budget is proportionately almost identical to that for fiscal years 1980 and 1981, and will allow funding of about 30 to 33% of approved competing new and renewal grant applications.

At present it is estimated that the dollars allocated to research in the neurosciences (basic and clinical) total about $400 million, or 6% of the total U.S. expenditures for health, research and development. Of this total not more than 40% is for "clinical" neuroscience research. In the United States, the NINCDS accounts for nearly two-thirds of the total for neuroscience research, with NSF and NIMH contributing about 5% each. It should be noted that these figures do not include the contribution of private industry.

Adequacy of Funding

Dr. Tower was emphatic in stating that this level of funding in the United States is far from adequate. The situation in Canada is even more disconcerting. The total funding for neuroscience research by government agencies in the U.S. is estimated at $400 million. On a relative population basis, the funding by the Medical Research Council of Canada should be $40 million. The actual figure is probably less than one-third this amount.

Clearly both the total amounts and the portion devoted to clinical investigations are not commensurate with the problems to be solved. For example, it is estimated that Alzheimer's disease and related dementias affect 15% of the U.S. population over age 65. Nursing home care for such patients costs approximately $10 billion annually, whereas research funding is only 1/1000th of that amount at $10 million per year (from all U.S. sources). Another example, taken from NINCDS data, is the prevalence of all neurological and communicative disorders, estimated to be 20% of the U.S. population with an annual cost to U.S. society in excess of $65 billion, compared to an annual research investment of less than 0.5% of that amount.

Dr. Tower identified several other problems related to the adequacy of funding:

- The increasing obsolesence of biomedical research instrumentation and research resources. It is estimated that at least $75 million is needed for updating.
- Escalation of indirect costs. From 1966 to 1979 direct costs in constant dollars for U.S. biomedical research have risen 35%, whereas indirect costs (overhead) have risen 350%, or ten times faster.
- The state of academic research. Concern has been expressed over the problem of translating scientific knowledge into useful products and applications. There are dangers in the trend toward academic private corporations, particularly the influence on the choice of research to technology, problems of secrecy, and threats to the quality of leadership and to morale of research teams.
- Problems in budgeting for large scale research projects. How does one determine priorities in budget allocations for such large scale projects as positron emission tomography research (a $10 million program recently launched by the NINCDS) or co-operative clinical trials (like the NINCDS evaluation of the extra- to intra-cranial arterial anastomoses for TIA's and stroke or of plasma-

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pharesis for Guillain-Barre syndrome), each of which costs $5 million or more to conduct? These are very significant bites out of an already inadequate budget, yet one is reluctant to ignore new leads or to omit needed evaluations of clinical applications.

- There are clearly major health problems and needs still to be addressed. The list proposed by Dr. Tower included the following:

  In technology: increased sensitivity and resolution, non-interventive monitoring techniques, methods for cell isolation and characterization, and better interfacing of the CNS with neural prostheses and application of microprocessor feedback techniques.

  In research: slow and latent viruses, neuroimmunology and neurogenetics, sensory transduction mechanisms and problems of pain, neurotoxicology, CNS growth and development, regeneration and plasticity, neurochemical circuitry, neural peptides and neuroendocrinology, development of speech and language in infancy and childhood, genesis and prevention of neural tumors, mechanisms in stroke and CNS trauma, and better diagnostic and screening procedures for disorders such as multiple sclerosis, Huntington's disease, etc. Many other important problems could be added to this list.

How to Increase Funding for the Neurosciences and How to Integrate Basic and Clinical Neuroscience Research

Dr. Tower emphasized that much hard work is required to increase funding for neuroscience research. We must increase public awareness of the needs for research on disorders that are not particularly popular and sometimes even distasteful to the public (e.g. stroke, deafness, epilepsy). We must involve the media effectively and seek the help of interested or potentially interested prominent public figures. In addition, grass roots pressures on funding bodies are a key element. And the private sector - academic, philanthropic (private and group) and especially industry - must be involved. Current priorities in research funding must be shifted to the neurosciences; and the key is to stress underfunding in terms of the needs and societal burdens. The integration of basic and clinical neuroscience research comprises two principle facets. First, appropriate interfaces must be developed or strengthened. At the level of the academic university hospital, research must combine basic units with clinical services, plus cross-talk between basic laboratories and their faculty and the clinical groups. In addition, applications of clinical research findings to "routine" care in the settings of community hospitals requires adequate and aggressive outreach from and interchanges with academic centers. Secondly, there must be adequate teaching and research training. They are essential for a productive research environment and for future research manpower needs. The phenomenon of a declining entry of physicians into the clinical investigation arena has already been mentioned. We must learn to prosyletize effectively and early, by providing medical students with elective and laboratory opportunities, and we must provide research opportunities for house officers.

The research environment is extraordinarily important. There must be clinical research units, fellowship programs (for training the recent M.D.), academic career programs and research support opportunities (to equalize the decision between research or practice). The NINCDS is attempting to meet these needs with institutional training grants, teacher-investigator development awards, and new-investigator grant programs, but there must be, in many cases, supplementation for the clinical institution from private sector sources. One additional facet of the research environment is better solutions for the problems of human experimentation.

THE NEED FOR INTERACTION BETWEEN THE DIFFERENT AGENCIES INVOLVED IN RESEARCH FUNDING: DR. LOUIS POIRIER

The particular responsibilities of the provincial governments in education and in health must be taken into account in attempting to establish the most adequate mechanisms by which federal and provincial polices related to the funding of trainees and of research activities in health sciences may be more efficiently coordinated. In recent years provincial governments and their research agencies have become aware of their particular responsibilities towards the support of scientific activities. This is illustrated by the recently created "Alberta Heritage Foundation for Medical Research" and "Le Fonds de la Recherche en santé du Québec, F.R.S.Q.". These two corporations have acquired a rather larger degree of freedom in the management and the funding of awards and grants-in-aid programs. They are also involved in the support of the basic and indirect costs of research in health sciences.

In addition, the influence of volunteer agencies in the development and the funding of research in health sciences has greatly increased over the last decade. However, all these actions taken by federal, provincial and volunteer agencies may lead to duplication or even triplication of funding in certain areas of research. Although this type of non-concerted strategy may occasionally have a positive impact on research in a specific domain, other important areas of research, both clinical and basic, may be neglected in so far as adequate and stable funding is concerned. Therefore, new avenues should be explored to find or improve the mechanisms by which concerted action between all involved agencies can most effectively promote high quality research.

The development and/or the reorganization of provincial agencies and a better identification of their responsibilities in the funding of research are factors that make the timing appropriate to engage in an open dialogue with the objective to offer to the scientists grants and awards programs that correspond to their needs. The long term support of original and productive research, the financial security of career investigators, an adequate financial support for trainees and the availability of adequate resources in personnel and facilities represent some of the main goals that

should guide those responsible for the establishment of new policies and guidelines.

A closer co-operation between all funding agencies would lead to the establishment of more appropriate policies that take into account regional and national concerns and should also result in the formation of more adequate strategies and guidelines for grants and awards programs. In this respect policies and guidelines that the federal and volunteer agencies may wish to put forward could be more smoothly and efficiently enforced through a close collaboration with provincial agencies, in view of the fact that the latter may act directly on provincial departments who are primarily responsible for policy making in education and health.

Several of the principles mentioned above apply to research in neurosciences. Adequate awards for trainees and career investigators together with a fair degree of financial security are required to encourage well-trained neuroscientists to embark on long-term research careers. Several of the problems which challenge neuroscientists require both clinical and basic expertise and often a close interaction between both types of expertise. Therefore, team work must be encouraged in several areas of research in neurosciences and clear-sighted leadership is greatly needed. Finally it is essential that the actions taken by all involved agencies and partners responsible at different levels of funding converge in order to create the proper environment and secure adequate financial stability for research centers. Concerted action between the several partners involved at various levels of decision making is essential in order to determine the strategies that will most efficiently promote the quality of research.

THE ROLE OF DISEASE ORIENTED VOLUNTEER HEALTH AGENCIES IN RESEARCH FUNDING: DR. MICHAEL GRAHAM

In Dr. Graham's view the disease oriented volunteer health agency has a vital and pivotal role to play in the funding of neuroscience research. Research funding provided by the Multiple Sclerosis Society of Canada has grown from less than $300,000 in 1973 to over $1.5 million in 1980. Figures from the International Federation of Multiple Sclerosis Societies indicate that in 1980 approximately $30 million was distributed for MS Research and Training Grants on a worldwide basis. A total of 530 different projects were supported. 300 of these were in the United States; 50 were in Canada.

Dr. Graham emphasized the importance of involving volunteer workers at the grass roots level. The success of organizations like the MS Society is largely due to the contributions of this type of individual.

Using the MS Society of Canada as a model, Dr. Graham reviewed the organization of a volunteer health agency. The MS Society has a national board of directors and a small centralized staff. However, much of the activity is carried out by seven regional divisions which have considerable autonomy and are free in many respects to determine their own methods for fund-raising. In addition, there are 50 local chapters, made up entirely of volunteer members.

However, Dr. Graham stressed two areas in which he felt there must be centralized control. One of these was in the allocation of research funds and the other was in the area of corporate and foundation fund raising which Dr. Graham indicated required specialized skills and a very personal approach. Of the funds available at the national level, a minimum of 80% are used to support research projects.

NEW DEVELOPMENTS IN NEUROLOGIC DIAGNOSIS AND TREATMENT: DR. PATRICK McGEER

The application of new knowledge and technology to the problems of clinical neurology and neurosurgery was discussed by Dr. McGeer. He reviewed several fields in which recent or anticipated developments are likely to have a major impact on the clinical neurosciences. Some of these represent new approaches in diagnosis while others may lead to exciting new developments in the treatment of neurological illnesses.

The first example discussed by Dr. McGeer was positron emission tomography. This is now being developed at several centers in Canada and United States. Although the costs are extremely high, the potential applications are very exciting. Basically, PET scanning provides us with a method to carry out "in-vitro autoradiography". It gives us a view of the brain at work. So far only the relatively easy things have been done with PET scanning, but already valuable information has been obtained in the fields of stroke and cerebral block flow and also in epilepsy. In the future it is quite likely that PET scanning will provide important information concerning neurotransmitters and receptors for transmitters and drugs.

Another major development in diagnosis is likely to be nuclear magnetic resonance scanning. The application of this technique to clinical problems is still in its infancy. Although the technology has been utilized for sometime in the field of basic chemistry, so far there is not a single center in Canada which has begun to develop clinical applications. NMR scanning is potentially capable of providing information about brain chemistry which even PET scanning cannot provide.

A third possible development in diagnosis involves the use of nucleic acid probes to examine the nucleic acid make up of an individual and to match it with patterns of inheritance. This could lead to major developments in the study of inherited neurologic disorders and might help identify specific enzyme deficiencies responsible for many of these diseases.

Turning to possible new developments in therapy, Dr. McGeer cited interferon as an example. So far the limited world supplies of this substance have been almost entirely committed to therapeutic trials in malignant disease. However, it is possible that an equally important application may be in the treatment of autoimmune disorders. Present evidence

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suggest that one of the actions of interferon may be to enhance activity of TS cells and thereby inhibit B cells, which may be the ones responsible for the autoimmune disturbances in disorders such as multiple sclerosis and myasthenia gravis.

The possibility of transplanting embryonic brain tissue to replace neurons which have been destroyed by disease is another potentially exciting therapeutic approach. Because the brain is an immunologically privileged organ it is possible to transplant immature neurons and have them grow and survive in the host brain. Whether they establish synaptic connections and develop normal functions is not yet determined. However, the possibility of replacing specific groups of neurons in disorders such as Parkinsonism or Huntington's Chorea certainly exists.

Dr. McGeer also discussed the potential use of proteinaceous trophic factors in treatment of neurologic disorders. A number of trophic factors have been identified in the peripheral and autonomic nervous systems. Almost certainly central nervous system neurons receive trophic influences as well and it is possible that some disorders may result from loss of these normal influences. Identification and purification of these factors could lead to new approaches for replacement therapy.

While admitting that some of these examples are still very speculative, Dr. McGeer emphasized the importance of presenting exciting new concepts and techniques if we are going to be effective in convincing individuals and organizations to provide funding to support the clinical applications of neuroscience research.

THE ROLE OF UNIVERSITIES AND INDUSTRY IN FUNDING NEUROSCIENCE RESEARCH: DR. KEITH COOPER

In Dr. Cooper's view, the universities have a major responsibility in supporting research in the neurosciences. If new developments over the next 10 to 20 years lead toward an understanding of the physical and chemical mechanisms of the mind and human behaviour, the responsibilities of the universities will become even greater. It will be necessary to develop increased awareness of the ethical implications of the research which is being done.

Dr. Cooper advocated use of the word "education" rather than "training" of neuroscientists. The universities' role must go beyond mere training. The universities must enable the budding neuroscientist to develop his analytical, critical, and synthetic capabilities to the maximum. They must provide the appropriate milieu and insist on rigorous and high standards in research. To attract good young people into the field, the universities must provide strong leaders and must also consider the problem of the employment opportunities which exist at the end of the education process. Universities should also provide leadership to help further breakdown the barrier between basic sciences and the clinical world. Dr. Cooper stressed that clinical science is not a separate field but really represents the application of scientific principles to a different class of problems.

With respect to industry, universities have a responsibility to provide scientists who will use their expertise to work on individual applications. At the same time industry has a responsibility to the universities to assist in the funding of education of scientists. Dr. Cooper felt that industry should always provide a portion of the scientists time free for "curiosity oriented research".

DEVELOPMENT OF THE INTERFACE BETWEEN BASIC AND CLINICAL NEUROSCIENCE: DR. JOSEPH MARTIN

Dr. Martin emphasized the importance of applying new advances to clinical neuroscience but identified several problems which exist in attempting to develop this interface. He referred to figures quoted earlier which indicate that the number of research grants being awarded to clinically trained investigators is diminishing in comparison to awards to "pure scientists" with PhD degrees.

An individual who is attempting to develop a career as both a physician and a scientist is faced with many tensions and insecurities. Some of these are related to obvious economic problems. There is still a significant disparity between academic and clinical incomes. In many cases a clinical trainee who elects to undertake further research training is faced with a substantial drop in salary from that of a clinical resident to a post-doctoral fellow. In addition, there seems to be a general feeling of pessimism amongst clinical trainees regarding the availability of research funding and the actual commitment of society to research.

Dr. Martin identified some of the differences which he perceived in mechanisms for research funding in Canada and the United States. In the United States the funding period for new and renewal research grants is generally longer than in Canada. New MRC grants are usually funded for a period of two years and this often places inordinate pressure on a young investigator to establish his laboratory and produce results in time for his first renewal application. A definite positive development in the United States has been the recent increase in the number of teacher-investigator awards, although Dr. Martin emphasized that in most cases these awards have to be supplemented by departmental funds to make them attractive to young investigators.

As possible solutions to the problem of providing an adequate number of physician-scientists to work at the interface between basic and clinical neuroscience, Dr. Martin mentioned the development of combined M.D.-PhD programs in a number of medical schools. These provide students with an opportunity for an indepth exposure to science at an early stage in their careers. The need for an increased number of awards as well as an increased level of funding per-award for the clinical trainee undertaking research training was emphasized further. Finally, the benefits of recruiting full time PhD scientists to clinical departments were reviewed, although it was recognized that this

approach introduces a number of logistic problems.

The final discussion was opened by Dr. John Desmedt who drew some comparisons between the systems for funding neuroscience research in Europe and North America. He described the North American system as a more "open" one with much more consultation and competition occurring between various research proposals. Once he has obtained funding, the European investigator is often not faced with the same burden of writing new research proposals at regular intervals. Yet, the economic squeeze is being felt even more in most European countries where increased demands for clinical service are being placed on young investigators. Dr. Desmedt emphasized the importance of encouraging people with clinical training to become involved in research and indicated that this was one mechanism of ensuring that research relevant to clinical problems continues to develop. Like the other speakers, he called for new and innovative approaches to subsidize the person with an M.D. degree until such time as he has acquired sufficient experience to undertake competitive research.

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