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KEY CHALLENGES FOR MEDICAL RESEARCH IN A SCEPTICAL AGE*

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It is a great pleasure to be asked to honour with you the name of Stanley Wilkinson, the founder of your Society, and the first orthodontist in Victoria. Your President has related his great human, personal and professional qualities, and, not having known him, I can add little to this. However, it is a special pleasure to deliver this oration in the presence of two of Stanley Wilkinson's sons, one a member of your own Society, and one a colleague with me in the field of medicine. I also know little of your profession, but am sufficiently familiar with the importance of specialization in my own discipline to realise its equal value for yours. Your Society undoubtedly has been crucial in the development of high professional standards in Australian orthodontics, and furthermore fulfils a most valuable educational role. It is likely that Stanley Wilkinson foresaw most of these things when he founded your Society, and the large attendance at this Congress, together with its clearly international flavour, would undoubtedly have given him much pleasure, and have vindicated his faith and judgement.

I have three purposes in my oration here tonight. The first is to tell you just a little about the kind of medical research which we do at the Walter and Eliza Hall Institute. The second is to make some remarks about the key challenges for medical research in the near future. The third is to talk in fairly general terms about the role of science and the attitude of society to it.

Research at the Walter and Eliza Hall Institute of Medical Research

In Australian terms, the Hall Institute is thought of as a big Institution, and indeed, with a scientific staff of about fifty graduates and a total staff of about one hundred and forty, it is the largest Institute of its kind in Australasia. Nevertheless, it is only small to medium sized in world terms. This being the case, and it being clear that anyone seriously engaged in medical research must think internationally, we have decided to specialize quite considerably in our work. In fact, about three-quarters of our work relates to that key cell in the body, the lymphocyte. These cells have a vital, dual role in the body's defence against disease. First, they are the immunological policemen that guard the body against infectious micro-organisms. Their attack against viruses and bacteria leads to the production of antibody molecules, which sometimes help in the conquest of the original infection, but, more importantly, prevent reinfection with the same micro-organism in later life. Secondly, the lymphocytes also have the job of immunological surveillance. This means patrolling the tissues and destroying cells that have mutated and which might be pre-malignant.

We have recently learned that the body's defence depends on two completely different kinds of lymphocyte, which we call T and B lymphocytes for short. The T lymphocytes are derived from the thymus, and they have the chief responsibility for surveillance against cancer and for the rejection of organ grafts that takes place when transplants are not protected through the use of immunosuppressive drugs. The B lymphocytes, derived from the bone marrow, actually manufacture the protein molecules called antibodies which circulate in the blood stream and protect against reinfection. In many immune responses, the two cellular systems actually collaborate in the defence of the body.

Unfortunately, in many cancer situations in both experimental animals and man, the T and the B lymphocyte systems seem to work against each other. The T lymphocytes mount a cellular immune attack against the cancer, but the B lymphocytes manufacture antibodies which are, for certain technical reasons, not strong enough to kill the cancer cells and which may actually block the effective working of the killer T lymphocyte. Therefore, key research projects at the Institute are designed to gain better understanding of the mechanism of action and activation of the T and B lymphocyte systems, with the long range

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hope that it might be possible to learn so much about the two categories of cells that their relative performance can be appropriately manipulated in clinical situations, including cancer, autoimmune diseases and organ transplants.

About fifty percent of the Institute's work thus relates purely to basic biology — efforts to understand the physiology and biochemistry of the cells of the immune system. Fifty per cent is more applied in nature, and includes various efforts in the fields of cancer, autoimmune diseases and allied immunological problems. The Cancer Research Unit under Dr. Donald Metcalf specializes in leukaemia, and as well as having interests in leukaemia of lymphocytes is developing much new knowledge about leukaemia of the other great white cell family — the granulocytes. The Clinical research Unit, under Dr. I. R. Mackay, has responsibility for running a ward in the Royal Melbourne Hospital, and its primary commitment is to autoimmune diseases, particularly of the liver, kidneys and stomach. However, substantial projects in multiple sclerosis, biomedical computation and cancer immunology are also in train.

Challenges for the Wider World of Medical Research

The accomplishments of medical research to date could be looked at under three general headings, namely Preventive Medicine, Curative Medicine and Supportive Medicine. By preventive medicine one means measures such as immunization against infectious diseases, the realization of the importance of vitamins and good nutrition in the prevention of many diseases and the optimization of human potential, and the control of water supplies and hygiene. These constitute the best type of scientific advance, as the results are cheap and effective control of disease. By curative medicine, I mean those measures where a swift, decisive intervention yields a clear-cut termination of the disease problem. Here we can cite examples such as antibiotics for simple infections, surgery of a ruptured viscus or of a hernia; or radiation treatment of a skin cancer. Not quite as good as curative medicine, but approaching it in practical terms, we can mention replacement therapy, such as insulin treatment for diabetes, or adrenal hormone therapy for Addison's disease, which do not actually cure but which deprive previously fatal disorders of their former terror. The third area, that of supportive medicine, is also frequently the result of medical research, but involves measures that are often elaborate, long-term, expensive and at best only partially successful. One could mention procedures such as open heart surgery, kidney transplants, blood pressure reducing pills, psychopharmacological agents or cytotoxic drugs in leukaemia. These things are valuable, but of a different order of benefit altogether to the other two types of medicine.

What differentiates these three fruits of medical research? Clearly the chief variable is an understanding of disease mechanism. The aim of all medical research is to shift emphasis progressively from no effective treatment to supportive and symptomatic treatment, to cure and eventually to prevention. However, cure and prevention depend on basic understanding, and for very many diseases indeed this is still lacking. In other words, any research aimed at the major scourges which still remain, including cancer, heart disease, strokes, and the various forms of mental disorder, must include a significant component of basic or fundamental research. The catch cry of "relevance" which one hears so frequently today can be misleading. It could lead to millions or even hundreds of millions of dollars being expended on a mindless screening search through thousands of compounds that may have anti-cancer activity in some highly stylized mouse model; while threatening with fiscal starvation projects in basic cell biology, molecular genetics or immunology, which could in the long run give real clues about cancer causation. Society is best served when this nexus relationship between basic research and applied research is fully understood, and when the two areas are allowed to go forward in close parallel formation.

A final reason for putting great effort into research aimed at cure or prevention relates to cost. In general, at the level of society as a whole, preventive medical measures are rather cheap, and curative medical measures may be expensive over a short period of time, but both of these are very cheap in relation to supportive medicine. It is really the "halfway house" measures provided by medical research which have caused the disastrous escalation of hospital costs and health costs generally. I am not suggesting for a moment that these costs are not justified, and that supportive medicine does not have a very important role. However, the financial angle is worrying as the total medical bill now adds up to between five and eight percent of gross national product in most developed communities. The real cures or effective preventitive measures, able to be provided by fundamental research, could lead to economic savings of great magnitude.

Science and Society

One of the hallmarks of our society is an incredible information explosion. In western societies, people know a little about a very large number of things. This has resulted in a substratum of superficiality and oversimplification, which might not matter too much if it were confined to subjects which do not directly touch people's lives. The trouble is that the very techniques which spread superficial knowledge also act powerfully in shaping the political decision-making process. Consider the following example. A scientist gives a lecture to a lay audience about

his work. A normal 50 minute lecture runs to about 6000 words. The discovery, though not earth-shattering, deals with an important topic — maybe a new diagnostic for some form of cancer or a new idea about the cause of multiple sclerosis. The lecture is attended by an eager young journalist. Anxious to see his work as close to page 1 as possible, the journalist files a 300 word summary, with a catchy lead phrase such as "multiple sclerosis triumph in sight". The sub-editor, still a good man just doing his job, chops the article to 200 words and finds it a nice place on page 3. The headline which just fits nicely is "multiple sclerosis triumph" — the "in sight" has been conveniently dropped. This appears in a morning paper. For the rest of the day, the scientist's phone runs hot. All the other newspapers, television channels and radio stations want confirmation and elaboration. The scientist, a little confused by this unwanted popularity, nevertheless tries his best. He spends from ten minutes to half an hour with each interrogator and also sends them all the full text of his lecture. The result is still the same. The media can cope with only the bare bones and have no use for the qualifying concepts. Radio and television may pare the 200 words down to 50 or 100. Next, the wire services take up the running. The story becomes world news. From Acapulco to Istanbul to Tokyo the new breakthrough in multiple sclerosis is hailed.

How could this scenario be improved? By the man not giving the lecture in the first place? How, then, is he to fulfil his obligation to the public that supports his work? By lectures delivered in very low key, and with ultra-cautious wording? Perhaps. By the preparation of written summaries tailored specifically for the press? Certainly; but there is no guarantee that *this* is what the press will use. Each journalist has his pride, and feels that his story must be unique and different. By insisting that the press ring back and check the story? Certainly again, but this cannot always be achieved. In any case, the problem goes deeper than mere technique and personality, and it is pointless to lay the blame only on the media. The root of the problem is in the necessary, enforced data reduction. The speaker himself has used a synthesis and has reduced by a factor of 20 the monograph which he has written, or could have written on the subject. The 100 word radio news item is therefore less than one tenth of one per cent of the original information. It *has* to be *thus;* there is no other way; the problem is without solution if free societies are to have access to the information that they require to run *as* free societies.

I have gone into this example at some length, because I believe we are dealing with a general problem. Most people who are expert in a branch of human learning or activity have come to have reservations about the media as regards that branch, but it is human to still be influenced by the media in all other areas. In other words, our opinions and attitudes are constantly being moulded by information services known to be something less than authoritative.

How does all this affect the community's attitude to science? — it is nearly inevitable that this will be an oversimplified one. After World War II, which indelibly imprinted the power of science on the public consciousness, there was a massive build-up in world scientific activity — a research boom, if you like. Cold war politics dominated some aspects, but in general few doubted that the advances in medicine, transportation, communications and consumer products arising from the science boom would help mankind to fashion a better future. How that bubble has burst! Today the headlines scream of uncontrollably rising medical costs, pollution and environmental decay, overpopulation, countless road accidents — and frequently the scientist is blamed for the lot! Add to this the disturbing thought that science is at least partly to blame for the declining influence of religion and a materialism related to ever increasing consumption, and you have what might be termed an anti-science bandwagon of major dimensions. The oversimplified hope that science would solve all problems has given way to an equally oversimplified and irrational despair about man's future. The road accidents, the sewage in the Bay, a baby born without arms, these are *news* and *rightly* so. But what of the polio cases, down from 2700 in 1951 to one in 1971? What of the tuberculosis sanatoria closed down through lack of custom? What of lives made richer and minds expanded through universal education? These are not news. We wring our hands over the miscarriages of science but take its benefits for granted.

The first thing to realize about this bandwagon of pessimism is that it is nothing new. Sir Peter Medawar noted in a recent article that in the first half of the seventeenth century, the mediaeval world picture of Elizabethan England had lost its power to satisfy and bring comfort. Jacobean melancholy was the new vogue. Francis Bacon's "New Atlantis" in 1627 was his dream of what the world might become if human knowledge were directed towards the improvement of the worldly condition of man. Bacon was nonplussed at the fact that "men despair and think things impossible". He writes of "spirits obsessed by the obscurity of nature, the shortness of life, the deceitfulness of the senses, the infirmity of judgement". Then he turns to his great personal hope: a rebirth of learning and the concentration of human faculties to the overcoming of perceived difficulties.

Bacon speaks of "the knowledge of causes and the secret motion of things" and also of "the

enlarging of the bounds of human empire to the effecting of all things possible".

Brave words, these, yet Bacon knew little of science, his words were written before Isaac Newton paved the way for the rise of the experimental method. So, incidentally, was the agonized cry of Montaigne: "Que sais-je" — What do I know?

These voices were raised to inject a note of hope into a period characterized by philosophic melancholy and gloom. They were, together with Réné Descartes, the forerunners of the Age of Reason. Rational humanism, with its emphasis on human self-sufficiency and its increasing reliance on the scientific method became the dominant philosophic influence in the eighteenth century — and remained dominant for two hundred years. It is only over the last twenty to thirty years that a new trend towards unreason, symptomatic of a society that has lost faith in scientific humanism, has arisen. In theatre, in art, in literature and in politics there is an acute sense of human failure — a general and oppressive obsession with the inadequacy of man. But surely we need to remember our history. The span of civilized human existence represents one two-thousandth of one per cent of the period during which life has existed on this planet. We should be conscious of the fact that human history is just beginning, and one great thing about beginners is: they *can* improve. I agree with Sir Peter Medawar, who said: "To deride the hope of progress is the ultimate fatuity, the last word in poverty of spirit and meanness of mind".

Our age may be a sceptical one, but the options for constructive action are *still* greater than ever before. Science and technology, dominant signposts of the age, have brought us problems, but can bring, are bringing, and will continue to bring solutions or at least workable compromises. This *will* depend on positive attitudes, and the harnessing of educated minds, transcending superficiality and over-simplification, to the global problems of our day. Alfred North Whitehead realized the saving potential of trained intelligence. In 1916 he wrote: "not all your heroism, not all your social charm, not all your wit, not all your victories on land or at sea, can move back the finger of fate. Tomorrow science will have moved forward yet one more step, and there will be no appeal from its judgement". Like it or not, science will continue to shape our society and our future. Let us seek with optimism and boldness to use science towards ends that serve the human spirit.

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