stress caused by obvious financial injustice. I can foresee the time, if financial pressures increase even more, when it will be essential for those wishing to pursue research in academic medicine to be paid separately for their clinical duties, and it may be necessary even so to support scientific research by money raised through limited private practice or other sources. It may be either that or complete standstill and I would then have no doubt as to what ought to be done. The growth of private funding of research has not reached its full development, but in future this would depend on methods of raising money which have hitherto been frowned upon, e.g. lotteries. As long as the means are legitimate, anything which persuades the public to give money of its own free will would be welcomed by me, since I cannot see taxes on the gross national product being anything but a diminishing asset to medical research. It might be argued that those who had opted for a full time research career had the strongest case for support and that existing MRC and other units in hospitals should get priority, and further that new ventures should be financed only in this way. This would be a return to the starting point in 1920 of university medical units in London hospitals and I would regard it as the last solution to be tried and a disaster if the present growth and breadth of medical research which has been so hardly won were to be cast away.

Finally, research is based on and accomplished by application over continuous periods without distraction and many have regarded this as incompatible with the practice of clinical medicine. This means that more people are required in the field of clinical research related to patients than many recognize, since some of these people must have continuous time at their disposal to achieve anything, especially when young. Increasing pressures on time by clinical and teaching duties seem to be inevitable.

I am encouraged by the great increase in whole time appointments in teaching hospitals where the recognition of the need to produce work and standards of medical care to justify any special consideration is becoming much wider spread. Pressures on time mean that extra help will be essential and conjoined work with someone always in the laboratory will be ever more necessary. The position of non-medical graduates who are not in the basic scientific departments will require very special consideration, and I am sure that medical schools in particular will have to create special grades much as the research councils have done, so that people of high talent can be attracted, maintained and promoted in a career grade. Joint appointments are one solution, e.g. between physiology and medicine, and the only one which can be implemented fairly quickly without enormous financial burdens. Non-medically qualified lecturers and so on, or scientific officers, will otherwise add intolerable financial burdens but they are going to play an ever increasing role in clinical research. While we will all have to follow the principle of cutting out something in existence to start something new, it is going to be very difficult to do this without some new source of finance, for these posts will undoubtedly be extra to current establishments. I suggest therefore, that in our priorities we think about future financing of research and I believe that we will have to pay for it out of extra earnings since I cannot see any fresh governmental sources of income, not even through contractual work. It is more likely that government money will be earmarked as for cancer, cardiovascular disease, and so on, and experience in the USA where money has been distributed in this way in the face of over-all reduction of funds is sufficient indication (Peart 1973).

REFERENCES

Peart W S
(1970) *Proceedings of the Royal Society of Medicine* **63**, 383
(1973) Lecture given at the Royal Institution to mark the 25th Anniversary of the Foundation of Glaxo Volumes
Todd (Lord) (1968) Royal Commission on Medical Education 1965-58. Report. Cmnd. 3569. HMSO, London

Limitations on the Discovery and Supply of Medicines

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I doubt whether anyone here would wish to minimize the assessment of the value of new medicines in benefiting humanity in the last half century. The mortalities of the 1920s and 1930s are very different from those of today. Changes have occurred because new drugs have been discovered and developed and been made available for general use. Diabetes, a fatal disease before 1920, is controllable through a full life span. Tuberculosis is largely controlled. The period ranging from the discovery of the sulphonamides through penicillin and other antibiotics to trimethoprim, has made medical disorders, commonplace when I was a student and about which I was expected to be knowledgeable, virtually unheard of and quite probably largely out of the curriculum today. Immunization with effective vaccines has displaced

diphtheria and poliomyelitis from the list of common crippling or killing diseases. Some steps have been taken towards the control of neoplasms and mental disorders and there is a wide range of substances for symptomatic relief which make diseases more bearable or more tolerable if not in any way prolonging life. All these achievements depend on drugs which have been discovered since the 1920s, developed and produced on a manufacturing scale, and are now widely available.

What is to stop this progress going on towards an even happier world in which all the remaining diseases which still cripple or kill prematurely can be controlled? It is not as easy as it was, and from my position of research in the pharmaceutical industry I would like to pick on four reasons why it is not just a little more difficult but a whole lot more difficult, and why progress is slowing alarmingly.

There are technical factors and there are legal limitations; there are emotional limitations and, at the risk of repeating from a slightly different slant what everyone has already said, there are financial limitations. Let me take the technical ones first. The easy discoveries have been made. It is the difficult ones that have been left. In the nature of things research, particularly in the pharmaceutical industry, is confined to laboratory studies, investigations in animals, and only very secondarily, when there is something clearly likely to be of human benefit, can one take any potential new drug to any kind of investigation in man. The infectious diseases have largely been conquered because, for instance, the difference between tuberculosis in man and in experimental animals is sufficiently small for drugs discovered in experimental animals, or even *in vitro*, to be also effective in man. But to start finding a cure for rheumatoid arthritis in a laboratory is much more difficult. There is no certain exact counterpart of the disease in experimental animals. The pathogenesis is far from clear, which is a polite way of saying that it is not known, and there is no experimental approach to discovering a real cure, as opposed to palliative treatments. One has to use roundabout, circuitous and more expensive approaches.

Higher standards in research demand higher technical standards of equipment. Tools for research become rapidly more elaborate and complicated. Twenty years ago no pharmaceutical firm required a computer for its research; mass spectrometers, nuclear magnetic resonance spectrometers and gas liquid chromatograms were unknown. They now form a necessary part of the hardware of the research laboratory, but each such piece of equipment costs at least £10 000 to £40 000. Beyond that initial capital cost are the maintenance costs and those of technical and scientific staff devoted solely to the care of these invaluable instruments.

Not only the discovery but also the production of drugs is becoming more difficult and more expensive. The advance of standards of chemical analysis makes it possible to set standards of purity much higher than those of twenty years ago. This is all to the good from the point of view of having a more stable, standardized, identifiable medicine for the doctor to use and the patient to consume, but undeniably it makes it more difficult to devise the processes for production, more expensive to execute them and more costly to control quality effectively. In the last year or so an ominous new difficulty has arisen: the shortage of raw materials essential for chemical manufacture is beginning to pose a serious problem in the supply of all drugs and, if the world continues in the direction in which it appears to be heading, this problem may become much more serious. Quite simply, remedies will become unavailable because some essential ingredients for their manufacture cannot be adequately obtained. Effort and technical ingenuity must be diverted from the search for new drugs in order to maintain the supply of existing remedies.

A final technical difficulty results from growing social unrest, an impediment to research and production. In the last year I have spent more time dealing with the problems of emergency generation of electricity to maintain our research laboratories, then I have spent time on considering how to conduct research, for which I am responsible. Comment is unnecessary, for my experience is anything but unique.

Secondly, we are much delayed or obstructed in the development of new remedies by the enormous growth of legal requirements devised for the very proper, laudable and desirable aim of making drugs as safe as possible. Possibly there has been an overgrowth. Before the thalidomide tragedy the control involved in placing a drug on the market was relatively limited. Because of the thalidomide tragedy and the public reactions and emotions aroused, the pressure for drugs to be safe has grown enormously. It is not generally recognized that there is no such thing as a safe drug. If a drug is completely safe and innocuous it is probably ineffective. Drugs are powerful tools which operate on physiological processes. When swallowed, a drug has an equivalent action to the surgeon's knife, directed by its chemical structure to a particular tissue on which it will act in a selective way. It may be, as the knife, entirely beneficial, but as the knife in the wrong place can be enormously damaging or fatal, so the drug may cause severe damage. Drugs are, in the nature of things, never com-

pletely safe, and I have heard it said that there are no safe drugs, only safe doctors.

Obsession with the safety of drugs is very damaging from the point of view of the advance of therapeutic tools and therapeutic skill. Of course we want drugs to be as safe as possible. The methods by which one assesses the effectiveness of a drug must depend on the situation in which the drug will actually be used. Likewise, the proper criterion for testing its safety for medical use is ultimately whether it is safe in clinical use in humans, or, in veterinary practice, in the species for which it is required. The multiplication of experimental toxicological studies in species other than the target species has got out of proportion and I suspect that this is not wholly recognized except by those who are intimately concerned in such assessments. Dr Alfred Spinks (1974), Research Director of Imperial Chemical Industries, gave a splendid Jephcott lecture on the subject of research in a harsher environment. At that lecture he drew attention particularly to the multiplication of requirements for animal toxicology and quoted an instance concerning the submissions made to a registration authority about a single drug on which it was wished to proceed to clinical trial. This submission consisted of a stack of documents 15 feet high! The quantity of information required in minute detail about individual experiments and actions of individual compounds on individual research animals, multiplied by all the forces for data generation now available, leads to an unreadable and formidably large submission, and the value of such gargantuan documentation is legitimately questionable.

It is absolutely right that there should be a proper check and control on the introduction of new remedies to widespread therapeutic use and certainly to their free release on the market. But any official body assessing whether a drug is safe knows that if the drug is passed as safe and ill effects subsequently occur, then that official body will be in dire trouble. If, on the other hand, an official body decides that it is not safe to put it on the market, the drug never comes to the market. No harm follows so there is no trouble. It is the business of any good authority to avoid rather than to provoke trouble. If in doubt it is prudent to ask for additional experiment in animals, and if sufficient experiments are performed, there will in the end nearly always be some reason in some species for suspecting that a compound might be dangerous if used in man and so should not be so used.

An interesting study has been published recently (Wardell 1974) of the effects, on the one hand, of the American Food and Drugs Authority and, on the other, of the British practice which is more permissive and more concerned with the monitoring of adverse reactions in actual clinical use of drugs. Delays taken for drugs to reach the market are considered and the therapeutic benefit and loss to the community of early and late release are compared. Wardell's very careful analysis showed the difficulties of evaluating any policy in this field, but gave no reason to seek any greater restrictiveness than now exists in the UK. The importance of making a judgment of this kind is great. Otherwise we are wasting a large amount of labour and resources on collecting evidence which can only damn the drug and which will not add to its potential therapeutic use.

A third problem or difficulty in introducing new medicines arises from public emotional reactions. These take two forms. The first lies behind much of the safety legislation. The public is scared of drugs. It does not fully appreciate that effective drugs will carry hazards. One anxiety of this kind was mentioned in discussion earlier about whooping-cough vaccine. Public reaction is greatly influenced by individual cases and is not well adapted to balancing risks on evidence from a large number of separate cases. Journalistic presentation, and particularly television displays, lend themselves to strengthening the first influence, so that it is much easier to arouse fears of a vaccine because of an individual tragedy than to promote confidence in a vaccination programme because of an overall increase in the number of healthy surviving children.

Another way in which emotional reactions are troublesome relates to experiments on living animals. There is a variety of ways in which discovering of new drugs is simply impractical without experiments on living animals. Such experiments are regulated by an Act of 1876 and are subject to careful regulation by the Home Office, and much care goes into ensuring that they are humanely conducted. Such experiments are not a welcome activity, and it would be nice to dispense with them altogether. The expense of animal care alone is a powerful deterrent to unnecessary animal experiments. However, in the last few years there has been a growing outside pressure to stop such experiments. Bills have been brought to Parliament to amend the workings of the 1876 Act. Evidence has been sought about the use of this or that practice. A fund for the replacement of animals in medical experiments has been set up, and time has been taken in providing evidence to its sponsors, showing what experiments are necessary, and why. This continual pressure can become a serious distraction. Such time-consuming enquiries are perfectly proper, but every ventilation of the matter fans public emotion, is potentially a damaging

arrest of progress, and is a diversion from the difficult enough process of discovering new drugs. This situation has been looked after for more than a century with reasonable care and effectiveness; a general upheaval now, for no very good reason, is not helpful.

Lastly, these difficulties can be expressed in financial terms. The pharmaceutical industry earns the costs of its research. That is, new research is paid for out of the money made by selling drugs previously discovered. Recently Dr Spinks quoted the cost of discovering a new drug and bringing it to the market in 1952 as being £1 million and in 1972 as being £50 million. Inflation is galloping but it is not galloping as fast as that yet! A fifty-fold increase in the cost of discovery is only a restatement in monetary terms of what I have been outlining: we do not have our computer, our mass spectrometer, our NMR and all the rest of it for free and we do not do the toxicology demanded by Government Departments for free. All these together contribute perhaps the increase from £1 million to £10 million for the cost of the research in its own right, the remaining £40 million going on to the various additional stages in assessing whether a drug is safe, how it is metabolized and so on, never done, or only done minimally previously.

With the great rise in cost a business has to consider much more carefully how it will direct its research to maximize the chance of recouping the £50 million spent on discovering its new product. In the nature of things, this sort of pressure leads to concentration upon products which will have the maximum wide-spread world-wide sale, that is, on drugs for the diseases which occur most commonly and are most rewarding financially. One consequence of the very great pressure for expensive toxicology testing is so to force up the price of research as to narrow it into a limited number of channels in which one can hope to recoup these costs. The multiplication of tests in experimental animals, unvalidated tests, possibly in the wrong species, can only add to the cost of drug discovery and limit the range over which such discovery is made.

On the other side of the financial fence, there is much public feeling about the large profits made by certain pharmaceutical firms. I can only say that there is no guarantee how soon one will discover a major return on research investment. Large risks are involved on the expenditure side. I have yet to hear of a fund being set up for the relief of distressed pharmaceutical firms which conscientiously attempted to carry out research on the rarer diseases in the hope of finding a remedy, and went bankrupt. It is a case of 'Heads I win, tails you lose.' If a pharmaceutical firm makes a large profit it is said how iniquitous it is that it should have made money at the expense of suffering humanity. If it fails to recoup its research costs because it does its research in unrewarding directions and does not concentrate only on profitable markets it is said to be badly managed, it could not even manage to make a profit.

These are real difficulties. I am not sure how in Utopia research costs would be met, but in the present world I would not like to see research directed to the alleviation of disease crippled by irrelevant restrictions. The cost of research has to be reimbursed from somewhere or other. One cannot multiply toxicological demands without paying for them. Somewhere a balance must be struck and this problem solved. We must accept that there are no 'safe' drugs, only, I hope, safe doctors. In so far as research is becoming more expensive, means of financing it which are seen and accepted to be equitable must be devised. As always, the total resources are limited: let us be very careful to make the best use of what we have.

REFERENCES

Spinks A
(1974) *Proceedings of the Royal Society of Medicine* **67**, 969–978

Wardell W M
(1974) *Clinical Pharmacology and Therapeutics* **15**, 73-96

DISCUSSION

Professor Charles Fletcher (*Royal Postgraduate Medical School, London*) remarked that the subject was important because the public was involved in everything that had been said so far. The more educated the public in the needs of medical research the easier would be the lives of those involved in such research. At the moment there was a conflict of view about the matter between the so-called mass media, the Press and broadcasting authorities, and the medical profession. There was a mutual suspicion. The medical profession suspected the mass media of being interested only in scandal and one-sided views. The mass media suspected the medical profession of wanting to get together to hide embarrassing facts.

He was looking forward to the possibility of achieving some 'meeting of minds' on a continuing basis. He was hoping that an initiative might come

from the Royal Colleges to get together in small groups with editors and responsible people in the broadcasting services to see what could be done to arrange for such a 'meeting of minds'. In addition, he would like to see the medical profession provided with better training in dealing with mass media. At the moment the number of doctors who were talented at broadcasting was very limited, while the number of members of the profession who regularly wrote articles for the newspapers was equally limited. He wanted medical schools to recruit people who had become editors of medical school journals and arrange for them to spend some time with a newspaper to develop their skills and to be trained. Such people could provide accurate reports on medical topics. The same thing applied to broadcasting. It was an art which could be learned and the profession should encourage members to learn it. At the moment the professions were standing on either side of a barrier which was inhibiting them from working together and improving the public health by both prevention and treatment of disease.

Professor G P Lewis (*Royal College of Surgeons, London*) said that Dr Burgen had painted a marvellously glowing picture of the advances of medical research. During his talk he had been waiting to hear about the constraints but there apparently were none. If there were, could Dr Burgen tell the meeting about them?

Dr Burgen pointed out that he had left the constraints to Professor Peart. The constraints were intrinsic, and not scientific restraints. They were political and economic. They were constraints of the will. Professor Peart had said that in a time of money shortage basic research would be hardest hit. He was sure that was right. It was a decision people could make but they would be wrong to congratulate themselves upon having made that decision.

Professor Lewis asked whether Dr Burgen would regard the development of government policy on research as a constraint. He had in mind the type of government policy which had developed from the Rothschild Report.

Dr Burgen believed that such a policy was wrong because it was based upon a false premise. He believed it was not possible to draw a hard and fast line between using available knowledge and developing fresh knowledge. The whole thing was a continuing process. Knowledge available one year that was useful for applied work was useless the following year because better knowledge had been obtained. It was ridiculous to say, 'We know enough basic research, apply what we know.' That was the philosophy of the Rothschild Report, that there was plenty of knowledge around but some wilful obstruction to the using of it. He did not agree with such a conclusion. As he had pointed out earlier, once the X-ray was a practical possibility people had galloped to use it.

Dr Miles Weatherall pointed out that what had been done with the X-ray would not be possible today, with present concern for safety and restrictions upon the use of possibly harmful equipment. A great deal of knowledge was awaiting application but could not be used because of the precautions which had to be taken before its possible utility could be assessed.

Professor Engstrom felt that one of the constraints upon the advance of medical knowledge had come about through the introduction of drugs engineered by molecular biology. The constraint would arise because the arsenal of tools that were necessary to administer the drugs would be complicated.

Another considerable restraint would be the research costs involved in chemical drugs. He did not feel that the drug companies could meet such research costs. That meant that the public and Government would be involved. The time constant for assessing the beneficial effects of drugs and the long-term consequences would be closely involved.

He hoped that medical records would be kept for a longer period of time than at present because they assisted in assessing changes in the drug environment.

Professor Peart reverted to the subject of medical journalism. He felt that the real advances had come from the 'professional' side of communications rather than from the medical side. The medical profession was extraordinarily bad at communications. They did not think it was a worthwhile occupation. That was not so. He felt that there should be communication at all levels and particularly at Parliamentary level through an extension of the Select Committee procedure. He envisaged some system, perhaps under the ægis of the Research Council, by which there could be a regular exchange of views with those responsible for presenting programmes to the public.

He thought that the attack upon the spirit of scientific inquiry was not confined to science. It ran through the universities as a whole. Public relations in universities were not at a high level. If the spirit of inquiry in universities was replaced by a practical study of known knowledge those responsible would be doing themselves and civilization such a disservice that they would deserve anything that happened to them.

Dr J K Butler (*High Wycombe*) pointed out that one restraint not so far mentioned involved the use of volunteers. Volunteers were sometimes needed to test a potentially dangerous drug, or to be involved in a situation calling for cardiac catheterization as a means of testing whether the drug was having a pharmacological effect. Many academic centres were willing to carry out such experiments while others were against the idea.

Another problem arose with drugs which were potentially dangerous or addictive. Historically, radical new treatments had been given to patients close to death. If there was a new immunological treatment for cancer, it was usually given to patients who were obviously dying. When was it reasonable to give such treatments to patients who were not near to death?

Dr K M Townend (*Bristol*) dealt with communication and education. It seemed obvious that there were those in the profession who were not quite such good clinicians as they had once hoped to become, while there were others who were closer to their fellow human beings than they once had felt inclined to become. There were some who were not such good teachers, or so it would seem by the products of their work, as they had tried to become. He would welcome any suggestion that the public should become more fully aware of the means of education, even though they might not be able to apply themselves to taking advantage of such education. He felt it was possible that as the profession became slightly more eclectic it was doing patients a disservice. He would welcome a more balanced panel of television programmes.

Mr M H Gough (*Radcliffe Infirmary, Oxford*) recalled that Sir George Godber had mentioned that one group claiming extra resources would only obtain them at the expense of others. Could the panel suggest some method whereby the constraints, spatial and financial, could be dealt with without leading to an increasing sense of frustration in the scientific community?

Dr Townend felt that most members of the profession would welcome the idea of furthering their understanding of disease and disease processes and extending the possibilities of better community and individual health. All would welcome the idea of medical statisticians furthering their interests simultaneously. On the one hand, he wondered whether doctors were feeling that they ought to say 'Yes' to requests from such statisticians while on the other they felt that they ought to say 'No' because of the emotional impact of the situation.

The Chairman (Sir Brian Windeyer) felt that what Dr Townend was saying was that there was a necessity to balance benefit against detriment. His particular interest was radiological protection. In that area there was a great deal of apprehension and so much known damage that the whole philosophy of radiological protection had to be based on balancing benefit against detriment.

Sir George Godber, replying to Dr Gough, said that there were many things which were practised simply because people had become addicted to their use. He instanced standardization of the first record sheet used in hospitals. That had been suggested a long time ago by a committee chaired by Professor Tunbridge. There had been heated objection to it. Standardization then could have effected savings running into six or seven figures. Long-stay periods in hospital and a determination to use the more expensive variants of a particular drug were further examples of increased cost.

The bulk of the money spent in the Health Service was not spent on highly expensive drugs but on the frequent use of quite common drugs.

Taking up a point raised by Dr Burgen, he said that if it were true that Rothschild had implied that we should not go on looking for further knowledge but simply apply what existed, then he could not understand why the MRC budget had not been transferred to the Department of Health rather than only one quarter of it. Further, that which had been transferred was still being spent on the sort of things it was being spent on when it went direct to the MRC. Remembering what Dr Weatherall had said about the cost of producing new drugs, he wished that the world was putting a bit more effort into producing things which would deal with diseases such as onchocerciasis, filariasis, schistosomiasis and other diseases which affected large numbers of poor people who could not afford to pay for expensive drugs. The battle against communicable disease had by no means been won. It was still the biggest battle of all. The knowledge that needed to be communicated to Parliament and others not medically or scientifically qualified should not be limited. What the public and Parliament needed to know more about was the fairly routine stuff. There needed to be a much better understanding about things such as vaccines. All vaccines had small hazards attached to them. They needed to be understood. In Denmark that had been recognized and there was a system for dealing with such things. A much more confident and open relationship was needed between the professions, the Department, Parliament and the public.

Dr S G Browne (*Leprosy Study Centre, London*) was glad that Sir George had elevated the discussion to global affairs rather than considering it purely from a Western point of view. Those present at the symposium were unrepresentative. They represented an elitist, highly intellectualized section of the medical profession and as such they were a diminishing proportion of the world's population. Economically and politically they would have less influence in the future. Was there not a greater responsibility upon such people to try to advise foreign governments and those who were until quite recently in friendly relations with us, about the more adequate disposition of the gross national product so that they did not spend quite so much on armaments or even education as opposed to medicine and the application of existing knowledge to existing problems?

Should not their influence in such countries be used in training graduates from overseas to orient their work towards the investigation and solution of local problems rather than the production of impressive papers dealing with highly sophisticated and esoteric research directed towards diseases which were far commoner in the Western world than the diseases to which Sir George had referred?

Professor Peart spoke of the luxury medicine practised in the Western world but added that it was necessary to look at the problems of individual countries. The last questioner had raised a number of social problems. The Indian government, for instance, could be questioned as to the use of its funds in certain directions. There was the question of food supply and the growth of population to be considered. He could not altogether agree that people from overseas ought to be trained merely to return to their own countries to deal with the more common diseases.