PAPERS AND ORIGINALS

Science for Pleasure or Science for Profit?*

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I have chosen this subject because for the first time in my lifetime scientific research is being questioned. Does it benefit anybody? If so, whom? Is it worth the money spent on it? Is there too much or too little? Is it directed at the right objects? Is it too pure or too applied? I doubt if these were questions that interested Thomas Linacre. I doubt indeed if they interested anybody when Linacre was alive. But since Linacre had a lively mind, and since he was creative enough to have founded the Royal College of Physicians, and thus profoundly to influence medicine and science thereafter, I cannot but believe that had he been alive today he would have been interested in the answers.

There are two reasons why these questions are now being asked—economic and moral.

Economic Reason

The last war was won by science and technology. After it there seemed little doubt that the peace would be won in the same way. Therefore, Government support for research increased enormously. In 1945-6 expenditure on research by universities and the research councils was £5.5 million. In 1969-70 it was £145 million.

It was inevitable that these increasingly large sums of money should sooner or later compete with money for other purposes and be called in question. In the United States the accelerating cost of the Vietnam war, and the plight of the cities and of the underprivileged and the poor, emphasized that Uncle Sam's pocket was not bottomless. In Britain the recurrent financial crises and the determination of the present Government to cut taxation and Government expenditure had the same effect.

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Moral Reason

The moral reason has emerged gradually. Now that science has provided the knowledge that enables men to survive, with a fair degree of probability, in reasonable comfort and in reasonable health to the age of three score years and ten, it has, to a large extent, discharged its public responsibilities. It is now the disadvantages of scientific knowledge that obtrude on the public mind. The world is becoming too populous. Because people are financially richer they have motor cars; the green fields are displaced by motorways, bungalows, and factories. The factories pour their effluents into the atmosphere, into the rivers, and ultimately into the sea. So do human beings. The atmosphere becomes increasingly foul. Even outer space is ridden with the satellites and rocketry, and the moon has the litter of man's recent trips. But the greatest threat of all is atomic fission. It is odd that the lesson of Hiroshima and Nagasaki took so long. Perhaps we had got used to man's destruction. What was new was the insidious effects of atomic radiation.

Not only are there too many humans, too many of these are getting too old. The advances made by medicine in the last 25 years have enabled us to cure most of those diseases which formerly winnowed out the young and the senescent. The advances of surgery enable old organs to be replaced by new. One exception remains—the brain. So the overpopulated world may become more and more populated by old men and women stuffed with other people's viscera, but with their own senile brains. It is not surprising, therefore, that people have begun to ask whether scientific research is really a good thing.

Scientific Research

Scientific research may be approached from the point of view of the individual research worker and from that of society. What is the reward of scientific research: on the one hand, to those who prosecute it and, on the other, to those who receive the new knowledge?

I once heard Konrad Lorenz define scientific research as "play carried into adult life." Thus was expressed an idea which I had been fumbling with for many years. It is now 45 years since I began to do independent research. I have no doubt whatsoever about my motive. I do it because I

like it. It is fun. I adore trying to find things out, particularly when I am trying to answer questions which nobody has been able to answer before, at least to my knowledge. It is the same kind of pleasure that an explorer gets, or a rock climber who is doing a climb for the first time, or an artist who is painting a picture unlike any painted before, or a composer. Scientific work is, in fact, a form of creative art. It is a form of creative art in which the dominant motive is curiosity, a property of every child, but one which tends to atrophy with age and which is so often extinguished by pedants while he is at school.

The quality of adventure in scientific research was emphasized by one of the greatest of the Linacre lecturers, Sir Henry Dale. In 1948 he wrote a paper entitled "Accident and Opportunism in Medical Research." He pointed out what, indeed, should be self-evident—namely, that most great discoveries are accidental. I say it should be obvious, but perhaps this is only with hindsight. In fact, a discovery is only classified as a great discovery when it reveals a fact or idea that was hitherto completely unknown. Because it was completely unknown there was no way of finding it except by accident. Dale cited several. Three of them concerned diabetes mellitus. Perhaps the greatest of all, from the point of view of Thomas Linacre's profession, was the discovery of penicillin by Fleming in 1929.

Fleming was typing staphylococci. As he finished examining the colonies he had grown on his agar plates, he stacked the Petrie dishes on the bench in his laboratory, whose window opened on to Praed Street. Before throwing these plates away he took another look at them and discovered on one a mould. Around the mould the staphylococci had disappeared; 999 out of 1,000 microbiologists would have said to himself, "confound that contamination." But what impressed Fleming was not the mould but the fate of the cocci around it. He wondered if the mould could be producing something which killed the bacteria, and so he cultured the mould and preserved his plate in perpetuity. Cultures of the mould indeed produced a fluid which killed pathogenic cocci and protected mice against inoculation with them. He named the substance penicillin. Alas, his chemical collaborator, Raistrick, had no faith and so abandoned the search for purification when the going got tough. It needed the war, Florey's managerial genius, and Chain's chemical know-how to purify it enough for human usage.

My own adventures in scientific research were more modest, but were so exciting that they are still fresh in my mind. Were I to begin at the beginning with intermittent claudication and go on to the end, to my present preoccupation with platelet thrombi, it would take too long and prove too boring. In any case, the point I want to make is not what a magnificent array of epoch-making researches have come from Pickering, but what fun it was at the time, and still is in retrospect. I will give two examples.

Headache

When I was working with Lewis, Wilfred Trotter retired from practice. Lewis asked him to come and talk to his staff. Trotter spoke to the thesis that headache was due to increased intracranial pressure. Oddly enough there were no measurements, so I set out to make them. The evidence did not turn out that way. The measurements, however, showed an association between the cerebrospinal fluid pressure and the diastolic arterial pressure in patients with hypertension (Pickering, 1934). This was one of the clues that led me to the concept that the malignant phase is merely a manifestation of a very severe degree of hypertension (Wilson and Pickering, 1938; Pickering, 1939a), and thus eventually to the concept, once heretical, now almost accepted, that essential hypertension represents a new type of disease in which the deviation

from the norm is one of degree and not of kind (Pickering, 1968).

However, my interest in the mechanism of headache had been aroused. One day I acted as a subject for E. J. Wayne, who was measuring the circulation time by injecting histamine intravenously. I got a severe headache. What fascinated me was that the headache throbbed with the pulse and even reflected the irregularity at my wrist, for at that time I was smoking too much and had extrasystoles. Here then was a method of inducing a headache which had an astonishingly precise relationship with the pulse. It promised well as an experimental model, so I set to work (Pickering and Hess, 1933).

The headache began after the flush was fading, reached a peak, and faded away. It was greatly increased by shaking the head, suggesting a meningeal origin. It occurred on both sides of the head in patients whose cervical sympathetic nerves had been removed surgically, but only on the intact side in the patients in whom the sensory root of the trigeminal had been severed. It was relieved by reducing the arterial pressure and by increasing the intracranial pressure—for example, by injecting saline into the subarachnoid space or by pressing on a large cranial defect. It seemed, therefore, as though it arose from a pain-sensitive structure in the meninges supplied by the trigeminal nerve and intervening between the lumen of the arteries and the subarachnoid space. It is probable that this is the region surrounding the large intracranial arteries. These observations were subsequently taken further by Harold Woolf, who extended them to migraine, an affection, oddly enough, mainly of the extracranial arteries. I subsequently investigated many other kinds of headache (Pickering, 1939b) but only one, the lumbar puncture headache, came out neatly. This, it was clear, was due to leakage of cerebrospinal fluid (Pickering 1948). The deficit was of the order of 30-50 ml. This volume of saline invariably abolished the headache.

These investigations made me extremely familiar with the problem of headache, which has been invaluable to me subsequently as a diagnostician. Thus I was twice called in to problem cases in which a diagnosis of a low-grade meningitis had been made, and in which I satisfied myself that the headache had none of the characteristics of meningitis and in which the whole case for organic disease fell like a pack of cards when critically examined in detail. In both cases the illness was largely iatrogenic and both patients recovered after suitable encouragement and doctorly neglect.

Renin

The second adventure concerned renin. I had begun my study of high blood pressure with the simple faith that the nature of the increased peripheral resistance would become evident from a physiological analysis, in the method of which I had been splendidly trained by Barcroft and Lewis. There was no doubt that the arteries of the hand were narrowed. I showed that this was not due to overactivity of the sympathetic nerves. I also failed to find anything in the blood. There remained the possibility of a chemical agent which had become fixed locally. In 1936 Prinzmetal came to work with me. He had made similar observations to mine. My own observations had excluded adrenaline and pituitrin as possible agents. They both blanched the red faces of patients with essential hypertension without much effect on arterial pressure. There remained renin, a substance described by Tigerstedt and Bergman (1898) and only once subsequently confirmed. It had disappeared from the index of all textbooks of physiology except Tigerstedt's own book. I had tested renal extracts before. Now we set about it again (Pickering and Prinzmetal, 1938). Extracts tested on the cat under urethane or on the spinal cat were always depressor.

At that time, in order to set up a spinal cat, we had

to book the special laboratory which was used by all workers wanting a large kymograph and artificial ventilation. But I had myself some rabbits in which I had denervated one ear before producing hypertension by a modification of Goldblatt's method. I expected that if a pressor substance was released by the kidney, this would alter the differential between the vessels in the denervated and undervated ears. In fact the differential stayed the same. But it was much easier to test the extracts on these rabbits, because it was possible without anaesthetizing them at all, to make the injections into the insensitive ear and to record the arterial pressure indirectly through a capsule in the other ear. Our efforts were instantly crowned with success and we had no difficulty in confirming Tigerstedt and Bergman up to the hilt, adding to renin's chemical properties. We devised the first method for its biological assay by using a stable standard, a method which I regret to say was lost during the war years in the morass of American misunderstanding of the elementary principals of biological assay. I tried to get renin out in conjunction with Gordon Butler, but it was a protein and when purified became very easily lost. We failed to crystallize it, and I abandoned further efforts at the beginning of the war. After the war Peart came back to my laboratory and succeeded in isolating angiotensin and getting its amino-acid sequence.

However, the adventure in renin that I most enjoyed was its location. I asked Gordon to look into the question of renin's association with glomeruli. It had been alleged that the outer part of the cortex of the kidney contains no glomeruli, but contains renin. I suggested he should look at this and showed him how to cut sections and examine them under the microscope. With Cook and Peart, he demonstrated that in fact no glomeruli meant no renin (Cook, Gordon, and Peart, 1957). To proceed further it was necessary to separate glomeruli from the tubules. Passing the kidney through a sieve of an appropriate grade allows glomeruli through and fragments of tubules. Cook had tried picking the glomeruli up with a pipette but this was so slow that the renin had left for the solution in which the fragments were suspended. It occurred to me that if we could introduce magnetic particles of the right size into the kidney, we would be able to hook the glomeruli out with a magnet. This was what we were able to do and found nearly all the renin in the glomeruli (Pickering and Cook, 1959). We showed experimentally that the rest could be accounted for by transfer from the glomerular fraction to the tubular fraction.

Cook (1960) finally completed the story. He cut glomeruli in half under the microscope and showed that the renin was in the vascular pole and not in the tubular pole. By tremendous assiduity and technical expertize he was able to suck granules out of the granular cells described by Goormaghtigh in afferent arterioles and show that these contained renin, proving what that remarkable pathologist, Norbert Goormaghtigh, had surmised on histological grounds just before the last war.

What have these scientific adventures of mine yielded? To me, intense pleasure, moments of real exhilaration, and, perhaps, delayed senescence. I hope, too, that I have been instrumental in passing on to some young men a bit of my enthusiasm, and have taught them that scientific research is disciplined curiosity, and that the discipline has to be learned if one is going to excel, just as in any other game or skill. Perhaps, too, they have done something for improving the lot of the sick. I have no doubt at all that they have improved accuracy of thought and method in medicine, enabling physicians to manage their patients with greater precision. Perhaps they have contributed indirectly to the immense advances in the therapy of hypertension though, of course, here it was Paton and Zaimis (1949), and Barlow and Ing (1948) who put the compounds on the map, who started the new era. But, in all honesty, I have to confess

that the possibility of benefiting my fellow creatures was a part of my motive.

Science for Profit

As we saw earlier, scientific research has become big business, and many of the public are dissatisfied. It has not brought peace. It has not brought freedom from want. It has not brought freedom from hunger. It has not brought happiness. And it has brought all these new and unadmirable phenomena: the atomic bomb, radioactive fall-out, overpopulation, the increasing toll of civilian road accidents, an ageing population, and pollution. Shirley Williams (1971) has written: "For the scientist the party is over. These have been very good times, these past 10 years. Finance has been abundant and has been increased impressively year by year. Respect, even awe, has been forthcoming from the press and the public: until fairly recently no one has asked any awkward questions. On their side the scientists have done all that could be expected of them. They have produced some outstanding pieces of research, won several Nobel Prizes, and kept Britain in the front rank over a wide range of pure science. Yet there is growing suspicion about scientists and their discoveries, and a widespread opinion that science and technology need to be brought under greater control."

What the leaders of society would like to do is, firstly, to direct scientific research so that what is useful to the community will be done and what is harmful will not; secondly, to ensure that research yields a high economic return. In order to do so, they wish to divide research into the kind of categories that social scientists understand.

Direction of Scientific Research into Useful and Harmful

I seriously doubt whether this is possible. Scientific discovery is mostly unpredictable. I have little doubt that the parents of atomic fission, Thomson, Rutherford, and Bohr, did not dream that their discoveries would give man the means to destroy himself. When this became imminent, Bohr did his best to stop the atomic bomb. Nobody could have directed Fleming to discover penicillin, because nobody knew it was there. Despite the huge sums spent on cancer research we cannot yet prevent it except by such simple methods as cutting down cigarette smoking, based on information which cost a few thousands of pounds to get.

For the last quarter of a century psychiatric disease has been the great scourge of civilized society. Bodies like the Medical Research Council, private foundations, and the National Institutes of Health in America have spent vast sums and yet nothing much has resulted. The psychoses, schizophrenia, and manic depression are still as obscure as they used to be. I have no doubt that the recognition of the cause of psychiatric illness will come by some accidental discovery made by someone who is working on the fringe, or even on some unrelated topic, but who is aware of the significance of his discovery, as Fleming was. An example of what I mean was the discovery that the urine of certain mental defectives gave a green colour with ferric chloride, a reagent used to detect diabetes. It was this that led to the recognition of phenylketonuria, a hereditary disease, characterized by deficiency of a single enzyme concerned in the metabolism of a single amino-acid, phenylalanine.

The most that direction of research can do is to support work with certain objectives and direction. For example, during the war the cream of the neurophysiologists in this country were redirected to radar, to which they made large contributions. But this was really development, not research. For the method, and what it could do, was already known. It always seems to me rather absurd that the three leading

departments of physiology in this country—Cambridge, University College, and Oxford—should all be engaged in this single rather limited line, neurophysiology. By contrast, Pavlovian physiology is non-existent. I am sure that more could be done by encouragement and disencouragement to stop the overcrowding of some subjects and the neglect of others than is done at present. But alas for the planners, direction will be nothing more than folly.

High Economic Return

To ensure that research yields a high economic return is an obsession of Her Majesty's present government. Because of it, the Council for Scientific Policy has commissioned exercises by notable economists. All these have done is to show how difficult it is, in the short term, and on a small scale, to forecast what will be economically profitable and what will not. In the long run, and on a large scale, there is no doubt. The whole history of civilization and of manufacturing industry is the history of scientific and technological discovery, their interrelationships and cross-fertilization, and the ease and cheapness of making new and improved products.

A country like Japan deliberately sets out to manufacture in industries based on science and technology. It does not bother with textiles. It concentrates on motor cars, on ships, on electronic goods, and on a host of other manufactures which require scientific and technical know-how and skill. So Japan is quickly becoming the richest country in the world. From that position she will advance to the most powerful. Alas, the United Kingdom lingers. It lingers not because of bad science but because our leaders do not know how to use the excellent science that we have. Britain has never put its best brains into industry and commerce. The industrialists do not really understand how to harness science and technology in the service of creating wealth. The universities and the people they produce are interested in the distribution and consumption of wealth, not in its creation. In this case it is not science which is at fault. It is the attitude of mind of the leaders of thought, particularly in the universities, which ensures that scientific and technological innovations are not exploited economically in this country. Instead the profit goes to Japan, Germany, and the United States.

To my mind, the direction of science into channels yielding a high economic return is likely to be an unprofitable enterprise. On one side of the balance sheet, the costing of scientific research may seem simple. In fact it is not. Science tends to grow as a whole and it is difficult at a point of time to say which part exactly of the total effort has brought an economic reward. On the other side, costing is impossible. What is the value of human life, and what the value of peace of mind, or freedom from pain?

Quantifying the economic rewards of scientific research is an obsession with governments determined to employ managerial principles in allocating public money. The most succinct answer was Ashby's: "The wool cheque for the 90 mile desert* for one year would pay for the whole of scientific research in Australia from the landing of Captain Cook."

Research Divided into Categories

The first division was pure and applied, the winning of knowledge and its use. The second was research and development (R. and D.). Development consists of those processes between invention and exploitation. It can be a very complex, tedious, and costly process, as the recent history of

* The 90-mile desert in South Australia was of great interest because it could not be explained by lack of rainfall. The fault was shown to be mineral deficiency. When this was supplied fertility was restored and immense fortunes were made.

Rolls Royce and its RB 211 engine show. Both these divisions are sensible, so long as we recognize their artificiality. The newest fashion is to divide research into curiosity-orientated, mission-orientated, and action-orientated. The Department of Education and Science found it difficult to discover for me the first use of these terms, though they are now bandied about by officials, social scientists, and even distinguished administrators. The first time I heard them they brought vividly to mind the silver collections to which I used to subscribe as a boy to the Church of Scotland's Mission to the Jews. As I understand it, curiosity-orientated research is meant to represent the search for useless knowledge. Mission-orientated research is meant to represent research designed to fulfill a particular mission or purpose. And action-orientated research is research which will result in action.

As a research worker of over forty years' experience I can only say that these divisions and their names are nonsense. Despite what those who sit on their behinds in offices may think and write and say, all true research is based on curiosity. The satisfaction comes when new knowledge arises. No one worth his salt is uninterested in the new knowledge he gets. The whole of modern antibiotic therapy, manufacturing, and the scientific advances resulting from it, depended on the accidental contamination of a plate by mould. What was not accidental was the perceptiveness of the scientist to whom it happened. As Pasteur said: "Discovery comes to the mind prepared." No one knows where his curiosity will lead to—a particular mission or a particular action. It is true that once the first knowledge has been gained, then concentration of effort may accelerate development. The war undoubtedly accelerated the technical development of penicillin, as it did with radar, and as it did with the atomic bomb, but the essential research and its new potentialities were there already.

The purpose of such divisions is to simplify the tasks of administrators and social scientists. If research can be neatly subdivided into what are called "meaningful categories" then it is possible to plan and to cost with greater precision and to carry out research programmes. Social scientists can even do "research" on them. But the whole history of human endeavour shows not merely the folly but the positive danger of asking, and trying to answer, questions which are based on artefacts. The latest of these, enshrined in the term "mission-orientated research," is by far the most dangerous in being the most pretentious, and the least related to actuality. God preserve science and the British nation from it.

Some Conclusions

It may come as an unpleasant surprise to the people who financed my research that I did it for pleasure and that I regarded it as a game—an exciting, complicated, and highly sophisticated game, but a game none the less. Is this moral? Certainly it is. I worked extremely hard, never less than 60 hours a week, and I still work in the laboratory, for which I receive no financial reward. All great creative artists, musicians, poets, novelists, work at white heat because they like it. There is nothing reprehensible in enjoying one's occupation. Far from it; only in that way can one expect style. Those who do research to be with it, for prestige, for the public good, for self-advancement, or any other purpose other than pleasure, are bad investments. They seldom produce original work and they have often dried up by 40.

So if the public wants knowledge, then they must seek it from those who really enjoy getting it. This is one of the facts of life.

How can the public ensure that scientists work on problems that serve the public interest? The best way is to induce a

sense of national urgency, as in war, when all scientists really tried to help the national purpose. The best way to launch a neglected subject is to induce a really productive scientist to take it up and found a school. Academic surgery in the United States is entirely due to W. S. Halsted. In Britain we are the poorer for never having had a department of real excellence until Illingworth and Kay developed one at Glasgow.

To secure an economic return from scientific research demands two measures. The first is to ensure that scientists are interested in the application of their work to industry and manufacture. The chief public enemy is scientific snobbery, which is prevalent in universities and in research council staff. The existence of this was the reason for Sir Solly Zuckerman advocating the transfer of research councils to the appropriate service ministry. I doubt if such an act of sleight of hand would be effective in suppressing scientific snobbery. It needs a public outcry against it. It is a very real phenomenon. My service on the Medical Research Council convinced me that all scientific snobs thought their own research was fundamental or basic, and the other chap's was not. To do applied research or research directed to a commercial objective was only suitable for plebians. It was *infra dig.* All this vanished in wartime, when to kill Germans was noble, but it is back again with peace when competing with them in trade is not. National peril may be just as great, but it is not so easily seen.

An even more important requisite is that industry should know how to use science and scientists. The plight of an industry like ship-building is not only due to demarcation disputes and bad industrial relations, it is also due to bad management with minimal employment of university graduates. Nowadays the output of university graduates is such that many of them must seek employment in industry if they are to be employed at all. But few of them are fit; too many graduates are either illiterate or innumerate. Engineers cannot write decent English and therefore cannot communicate. Arts graduates have not studied science and therefore have no competence in dealing with science and scientists. It never ceases to astonish me that, faced with crisis after crisis since the last war, we still persist in the ridiculous habit of asking boys and girls to choose between arts and science at puberty. People tell me that this practice is dying, but, as head of a college, I interview every student who comes here and there are still too many who do. There should be none. In this practice we are alone among the wealthy nations; if we persist, we shall be wealthy no longer and we shall deserve our decline into bankruptcy and obscurity.

I have no doubt that administrators can tinker with science and scientists to their hearts content. They will achieve nothing until this radical fault in our educational system is remedied.

The Moral Issue

The present revolt against, and antipathy to, science is to my mind largely based on a misconception. The new ills of mankind are not due to the new knowledge but to the way in which that knowledge is used or applied. It was not the knowledge of what atomic fission would do, but the decision to use that knowledge to destroy human beings that was decisive. Overpopulation could be remedied in four generations if men and women were sensible enough to use methods of birth control which modern science has provided. Pollution is not due to science but to a failure to use science to keep the air and the water clean. And so with the other curses that we have inflicted on ourselves.

I find it truly remarkable that apparently sensible people should blame science for what is the community's failure to use scientific knowledge to social ends. On the moral issue of what should be done and by whom, science has nothing special to offer. As Christ said: "Render therefore unto Caesar the things which are Caesar's; and unto God the things that are God's." Science is concerned with Caesar's things, not with God's.

I have drawn attention to the moral issue because it seems to me to be by far the most important for the human race at a crisis in its history that is rapidly approaching. If man solves this, he and his heirs will survive and flourish; if not, they will perish. Science has no doubt furnished the tree of knowledge of which he has eaten. If he remains as evil as he is now, his eternal damnation is inevitable.

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