# Papers and Originals

## Medical Science: Master or Servant?*

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### Harvey and the Scientific Method†

If any testimony were needed to the unique position of William Harvey in the development of modern medicine, it would be sufficient to note that after more than three centuries new researches into his life and work continue to be made and have yielded in the last few years a quite astonishing harvest. Notable among them are the recent volume by Keynes (1966), so rich in learning yet so delightful to read, and that unique triumph of erudition and insight, the new transcription of Harvey's *Praelectiones* by Gweneth Whitteridge (1964, 1966), together with her interpretation of the manner and sequence in which they were written, so that we are now almost able to follow the trains of thought which led to the gradual revelation of the secrets of the circulation of the blood, in Harvey's mind.

As to his methods, there is no better source than *De Motu Cordis et Sanguinis* itself, and perhaps Harvey's own writings in reply to Riolan. Harvey described his work as proving the circulation of the blood "by reason and experiment." It is indeed the charm of *De Motu* to the present-day scientist that reason and experiment go hand in hand throughout, the experiment being carefully devised to prove or refute the hypothesis, the hypothesis having been derived from experience and the contemplation of data carefully observed, the perfect scientific method, in fact.

In spite of this, Harvey knew that in his day his methods and his conclusions were so unorthodox that they would be criticized and rejected by many of his contemporaries, and he said: "I fear lest I have mankind at large for my enemies, so much doth wont and custom become a second nature. Doctrine once sown strikes deep its root, and respect for antiquity influences all men. Still the die is cast and my trust is in the love of truth and the candour of cultivated minds." [1]

Harvey's contemporaries and successors, nevertheless, generally accepted his teaching, but failed to find any way of making it relevant to medical practice. This was inevitable at that time, but they might have been quicker to adopt his experimental methods in the pursuit of the further knowledge of physiology.

As to his practice of medicine, Harvey was considerably criticized during his lifetime, and it is interesting that Lord Conway warned his daughter, who was a patient of Harvey's, against him, in spite of his obvious esteem for Harvey's scientific merit.

John Aubrey said of Harvey: "All his profession would allow him to be an excellent Anatomist, but I never heard of any that admired his therapeutic way. I knew severall practisers in this Towne London that would not have given 3d. for one of his Bills and that a man could hardly tell by one of his Bills what he did aime at." Dr. Broun, a generation after Harvey, said that his discovery had "seemed to illustrate the theorie of Medicine, yet it made no improvement in the practice thereof" (Clark, 1964). Sydenham, in his various writings on clinical subjects, did not mention Harvey's work at all.

But before we pursue the results of Harvey's experimental work, let us end with John Aubrey's comment on his character. He tells how Harvey made him "sitt by him two or three hours together in his meditating apartment discoursing.

"He was very far from bigotry. Why, had he been stiffe, starcht and retired, as other formall Doctors are, he had known no more than they. From the meanest, in some way or other, the learnedst man may learn something. Pride has been one of the greatest stoppers of the Advancement of Learning."

Aubrey clearly recognized Harvey as a great man.

### Fruits of Science

There was, in fact, a period of more than 200 years before experimental physiology on Harveian lines can be said to have begun. Müller, Helmholtz, and, above all, Claude Bernard on the Continent, William Sharpey and Marshall Hall in England, and later Starling, Bayliss, and J. S. Haldane are names which come to mind, but the introduction of the methods of experimental physiology to clinical medicine is something which really belongs to my own time. Its development has been rapid and productive, so that today, all over the world, universities have their academic clinical departments, staffed for the most part with the descendants of Harvey, Bernard, and Starling, rather than the descendants of Sydenham and Osler, and engaged almost entirely in the application of the Harveian method to the investigation of bodily function and the manifestations of disease, in the course of which they have, as Harvey predicted, gained much from the study of nature's own experiments.

This has led to a new understanding of the scientific basis of medicine, comparable in its significance with Harvey's discovery of the circulation. The physiology and functional pathology of disorders of metabolism, of the heart, lungs, and kidneys, and of the digestive system, have all proved to be rich sources of study by these methods, and in some areas the physician has virtually taken over the role of physiologist.

Large and increasing funds from public and private sources have been devoted to medical research of this kind, and more and more persons have been attracted into careers in clinical science. The impact of science and technology has brought new skills and refinements into diagnostic methods.

On the therapeutic and preventive side of medicine we have, in my time, seen the virtual conquest of bacterial disease,

* Harveian Oration delivered to the Royal College of Physicians of London on 18 October 1967.

† This introductory section is somewhat abbreviated from the spoken version, which contained more material concerning Harvey's relation with the College of Physicians.

[1] The wording is my modification of Richard Asher's modification of Bowie's revision of Willis's *Transcription* and is near enough to a translation of Harvey's Latin in chapter VIII of *De Motu*.

including tuberculosis, and the prevention of poliomyelitis. Fatal diseases such as pernicious anaemia and severe diabetes are now controlled; cancer of the lung is known to be largely preventable. Modern anaesthesia and antibiotics, along with new technical cunning, have combined to make cardiac surgery a reality. Except in the most primitive parts of the world, plague is a thing of the past, and if malaria is not already eradicated it is for want of resources and not for want of knowledge. The overpopulation resulting from the conquest of disease could now be countered by modern means of contraception, which with little doubt will soon be further improved.

To this audience there is no need, and no time, for a full catalogue of the victories. One has only to think back to quite recent history, the plagues of the seventeenth century, the infant mortality of the eighteenth and nineteenth centuries, the deaths of Chopin and Keats and the Brontës from tuberculosis, to be grateful for the achievements of scientific medicine.

## Critical Survey

The adoption of the scientific method in the Harveian tradition by clinical medicine has been recognized by the appointment of about 43 wholetime professors of medicine or of therapeutics in the United Kingdom alone.[2] The growth of departments of academic medicine in the United States has taken place at the same time on an even larger scale. Their contributions to the understanding of disease are established, real, and secure, and they have helped to make possible the deployment of the discoveries of modern medical science, both in relation to treatment and in diagnosis. Yet we must face the fact that these departments have not been responsible for, nor even seriously involved in, any of the discoveries in therapeutics or preventive medicine which I have just enumerated.

The antibacterial action of the sulphonamides was wholly worked out in the laboratories of pharmaceutical industry, starting with Mietsch and Klarer and taken up by Domagk, though the original idea that dyes could be antibacterial stems from Ehrlich. From the sulphonamides, hypoglycaemic agents such as tolbutamide have developed, and a whole series of diuretics of the chlorothiazide class.

The antibiotics originally sprang from an observation of Pasteur and Joubert of 1867, but Fleming's findings of 1929, which he left undeveloped for 10 years, were then taken up by Florey and Chain, who isolated pencillin and demonstrated its effectiveness. Attempts at synthesis were an expensive failure, but better culture methods developed in American Governmental laboratories and by the Pfizer drug company made penicillin a practical success. From the penicillin idea comes streptomycin, discovered by Waksman and his colleagues in a university department, and developed by Merck. All the subsequent antibiotics have originated in industrial laboratories. None has depended on clinical scientific departments or on the kind of clinical science which they teach.

Isoniazid and para-aminosalicylic acid have arisen from the combined work of academic and industrial departments. The new penicillins have come from the Beecham Laboratories.

Poliomyelitis vaccines have been developed by non-clinical scientists.

Liver treatment of pernicious anaemia was an exception, coming as it did from Minot and Murphy in an academic medical unit, taking a rather long shot from animal work by Robscheit-Robbins and Whipple, which could have been quite irrelevant. These latter workers had suggested that there might be some "parent pigment substances" normally stored in the liver. In spite of this lucky and favourable beginning the hard scientific work of isolating vitamin $B_{12}$, the active principle, was accomplished by scientists in the pharmaceutical industry in Britain and the United States.

Insulin, as everyone knows, was first extracted in a physiology department, and almost stands alone as having resulted from good scientific reasoning. The discovery that carcinoma of the lung was caused by cigarette smoking was due to clinical observation, followed by a first-class study by the techniques of epidemiology.

The synthesis of cortisone was combined work between an academic non-clinical scientist and a drug firm—namely, Merck—done as part of a wartime programme sponsored by the United States Office of Scientific Research and Development. But Hench, of the Mayo Clinic, made a clinical contribution to the cortisone story which was of great importance, especially as he had to some extent predicted the results by clinical observation. Stilboestrol came from an academic non-clinical laboratory.

To continue the recital would be tedious, but the findings are essentially the same when we look into the origins of anaesthetics, tranquillizers, vitamins, antimalarials, antihistamines, hypotensives, sex hormones, and oral contraceptives. Not one originated in a department of academic medicine or therapeutics. Even D.D.T., so important to preventive medicine, was discovered by Müller, working for the Geigy company.

I must acknowledge here my debt to Dr. William Bain for helping to ensure that my information is accurate and for calling my attention to Professor Ernst Chain's Trueman Wood Lecture of 1963, which contains most of the relevant information.

## Ideas and Resources

If we are to draw any tentative conclusions from this survey of the origins of the control of human disease in our time, we might wonder whether the establishment of scientific clinical units interested in the exact study and measurement of the phenomena of disease has, like Harvey, succeeded in illuminating "the Theorie rather than the practice of Medicine," for the phenomenal success of modern medical treatment seems to have depended almost wholly on non-clinical, often non-medical, scientists, frequently working in, or in close collaboration with, the pharmaceutical industry. And it would be a serious mistake to think that the role of industry has been largely in the field of commercial development. A great deal of the basic scientific work, especially chemical isolation, analysis, and synthesis, has taken place there.

Ideas come from lucky accidents or from the inspiration of men of imagination. At the next stage, where the idea needs to be worked out, there seems to be a strong case for directing resources deliberately to the achievement of an objective, rather than devoting so much of our research potential to the investigation of observed phenomena of academic interest. In fact, both the Ministry of Health and the Medical Research Council have in recent years called together conferences and working parties with the object of seeing how money and manpower may best be applied to the achievement of specific objectives; for instance, in intensive coronary care, recurrent dialysis, leukaemia, and pyelonephritis. This may need resources not always to be found in academic and Research Council laboratories, and might require a major redeployment of Research Council funds. Where ideas have originated in the academic laboratory, collaboration with industry, not necessarily only the pharmaceutical industry, if required, should be sought early and willingly, not reluctantly and belatedly.

Some real discoveries have been made in academic clinical departments, often in the field of rare disease, such as primary aldosteronism, but the accurate study of function in chronic destructive disease of the lungs, the kidneys, and the liver has

[2] This includes the occupants of personal chairs in medicine and related subjects, such as neurology and cardiology, but does not include psychiatry, paediatrics, or preventive medicine, nor surgery, nor gynaecology, nor laboratory medicine, such as pathology.

sometimes seemed more akin to an absorbing hobby than a therapeutic exercise, though occasional and temporary relief to the patient may be a by-product.

It was predictable that the prevention of silicosis would not derive from refined studies of pulmonary function, and that lasting benefit in chronic renal failure could only come from something which would replace the kidneys—that is, transplantation—or take over their function—that is, repeated dialysis. These methods are now being developed and basic scientific work on the consequences of renal failure has been an important preliminary to their proper use.

Methods of resuscitation occasionally save lives worth saving, as in the treatment of cardiac arrest, but are all too often employed in keeping alive those who would by any possible standard be better dead.

Perhaps the most important therapeutic gains in which clinical scientific departments have played a part have been in the electrolyte field and in endocrinology (though few of these latter have been initiated there), and in cases where physician and surgeon collaborate in the accurate investigation and subsequent surgical treatment of defined conditions, as in cardiac surgery.

Perhaps it does not matter that the academic clinical departments of medicine and therapeutics have not contributed as much as one might have hoped to the treatment and prevention of disease. So much has been done by the non-clinical scientists, together with the drug firms, that the clinical departments have been left with the hard core of chronic disease in an ageing population, which is rather barren soil to cultivate.

## A Paradox

But here we come across what Rustein (1967) has called the paradox of modern medicine. The expectation of life in the United States has remained almost stationary for the last 15 years or so and has in fact fallen well below that of other countries, such as Sweden and the United Kingdom. Yet this is not just a phenomenon of the aged, for in males of 15 to 44 years, for instance, the death rate is notably higher in the United States than in Sweden for every major cause of death except suicide. At the same time the infant mortality has failed to improve as compared with other countries, and all this is despite the fact that federal expenditure on biomedical research in universities and hospitals[3] in the United States has increased during the last 20 years from $1m. to $1,000m.

To return to the clinical scientific departments, I have already acknowledged their contributions to the application of scientific discovery at the bedside. The very pursuit of research, moreover, provided that it is relevant, has merit in its own right in creating an atmosphere of intelligent inquiry; but in medicine the practising physician who is intensely interested in the diagnosis and treatment of the individual patient and responds to the challenge which every fresh patient brings has his own constant stimulus to intellectual inquiry and need not be ashamed if he finds the added burden of organized scientific research something of a distraction. A great deal of modern practice in medicine and surgery has been evolved by men whose researches were part of their daily clinical tasks. Cardiology and neurosurgery are good examples.

The situation in clinical research is bound to be different from that in the laboratory sciences which contribute to medicine. All clinical research is, and must be, applied research. To ask a protein chemist what use his work is going to be to mankind would be an impertinence, but we are entitled to ask *Cui bono?* of a clinical scientist carrying out investigations on patients. And we have a duty to pause from time to time and ask whether clinical science is wholly beneficial, or whether there could even be instances in which its influence was actually detrimental. For instance, has the obsession for measuring what are now called *parameters* in chronic organic illness led to the neglect of other and more important problems? Do the scientific clinical departments absorb almost all the research potential of our best graduates and thereby deplete the pool available for research directed towards current problems of really pressing nature, such as drug addiction, neurosis, oral contraception, delinquency, alcoholism, aggression, and the prevention of lung cancer?

Is the Harveian method, as interpreted by clinical science, ever really likely to yield therapeutic results? Has it already reached a point of diminishing returns? Does medical science, as taught in academic clinical departments, really develop the prepared mind? If so, why have not more of the ideas behind modern therapy sprung from these departments? Finally, is medical education too much dominated by the clinical scientists at the present time? Some of these questions it will be my endeavour to examine.

## Further Heresy

The demands of the clinical scientists for ever more expensive and sophisticated apparatus are justifiable if the things to be measured by the apparatus are relevant and important to the study of human health and disease, and if they cannot be equally well assessed by simpler methods, but no one who has been involved in the disbursement of funds for clinical research can come away without misgivings about whether time, talent, and money are sometimes squandered on the measurement of the trivial, the irrelevant, and the obvious. Given a new and expensive tool such as a gas chromatograph, an electromagnetic flowmeter, or a multichannel recorder of some kind, it becomes all too easy to find a subject for research; for there is bound to be something which has not yet been measured by these means. The need for thought, observation, ideas, and hypothesis, which form the hard work of research, recedes comfortably into the background for a year or two, while the research worker, supported by a grant and relieved of the much harder task of practising medicine, collects his results and has them analysed for him by a computer. One has the impression at times that the thought process starts with "What experiments can be done with these tools?" and that the "imaginative episode of thought" so essential to good scientific discovery has been bypassed. Medawar on scientific method should be required reading in all clinical scientific departments. And Harvey's *De Motu Cordis*.

It is only a very slight exaggeration of the truth to say that I have seen applications for an electroencephalograph to tell whether the subjects of the experiment are awake or asleep, and for a recording device to tell whether a baby is crying; and that I have recently listened to an account of scientific work which seemed to demonstrate beyond reasonable doubt that getting hot is closely correlated with sweating. No wonder that a friend of mine who has a gift for felicitous expression has distinguished between "ideas" research on the one hand and "occupational therapy for the university staff" on the other, and once referred to a research project as "squeezing the last drop of blood out of a foregone conclusion." I am afraid I am not one of those who would count it a triumph of modern medical science that it is possible to measure the blood-flow through the liver in a patient with mitral stenosis who is being exercised on a bicycle ergometer. There is no special significance in this particular example, which is only one of many that could be chosen. At its best this kind of experiment makes a trivial addition to human knowledge, at its worst another contribution to the already bulging archives of the Pappworth (1967) collection.

Research is supposed to train the mind into channels of scientific (and therefore respectable) thought, but does not this kind of research sometimes encourage the erroneous belief that

[3] Distributed through the National Institutes of Health.

only that which can be measured is worthy of serious attention ? "Not everything we count counts. Not everything that counts can be counted," was wisely said by Dr. Stephen Ross (Jason, 1966). And what kind of impact does the human guinea-pig make on medical students ?

But if we are seriously and in all sincerity to try to assess the debit side of clinical science, then unhesitatingly I would put among its greatest failures its almost complete neglect of psychological factors in disease, and this is my next theme.

## The Mind

The proper study of mankind is of eternal and absorbing interest, not because man is a chemical engine, as one scientist has told me, for that is an attribute which man shares with the amoeba, but because of the endless variety of the interplay of human personality, intellect, emotion, and motivation. That is what all great literature and great poetry have been about ; it is the raw material of nearly every interesting conversation, whether in the senior common room or on the Clapham omnibus.

Yet what is acceptable to read in literature is not always acceptable if it threatens to become an analysis of our own unconscious mind, and man has from earliest times built up an elaborate series of defences lest his carefully sublimated emotions and motivations come disturbingly into consciousness. The defences have taken various forms: the material walls of monasteries, nunneries, and colleges, for instance, where the intelligentsia could isolate themselves from the undesirable and disturbing contacts of everyday life. Sir Arthur Thomson, in his Harveian Oration of 1961, recounted how that wealthy scientist, Henry Cavendish, once met a housemaid on the stairs of one of his mansions and promptly had another staircase built so that this encounter could not recur.

Taboos have been built up and rationalizations and fantasies, of which the legend of the Garden of Eden is surely one of the supreme and most ingenuous of examples.

Freud tried to bring us up against stark reality, but, in spite of him, these defences are as clear in a medical school today as in any other seat of learning.

Walls have been built to segregate those who are mentally ill, but they had the great advantage of isolating not only the patients but also the psychiatrists, who, until the second world war, were almost never allowed in a teaching hospital.

Sex education was taboo until quite recently, and still is in many—perhaps most—medical schools, unless one includes under that term the anatomy of corpses, the study of venereal disease, and the chemistry of hormones. Not my idea of an acceptable introduction to the biology, psychology, sociology, and aesthetics of sex.

## "Clinical Material"

Patients, often hideously called the "clinical material" of teaching and research, have been drawn so far as possible from the lower social classes (everyone well brought up knows that the lower social classes have no emotional needs or feelings), and were, and still are, interrogated either in an almost open outpatient department in the presence of numerous students or recumbent in a hospital bed in an open ward ; conditions chosen with unerring insight to ensure that the psychological factors in disease, even if present, cannot obtrude and disturb the proper pursuit of scientific medicine. But to make assurance doubly sure, the ward round is conducted as a ritual, the chief followed by his numerous attendants.

The advent of the professorial medical departments, which should have brought with it new attitudes towards patients consistent with the new understanding of interpersonal relations, has in some instances merely reinforced the defences by a more refined and narrow choice of the "clinical material," by the abhorrence of private practice (thus ensuring that the patient cannot call the tune), and by the development of grand rounds to replace the ritual visits of former years. I have seen a patient wheeled in and demonstrated to a large meeting and wheeled out again without a single word being said to her—not even a word of thanks. Finally, the study of anything except organic disease is dismissed as unscientific. I have heard a research worker who has studied rheumatic disease for many years confess without apparent shame or embarrassment that the idea of investigating psychological factors had never been seriously considered.

## Psychological Factors

The advent of the psychiatrists, so long as they can continue to be classed as eccentrics and therefore isolated from the main stream of clinical teaching and research, allows for the continued segregation of personality and emotional problems.

If challenged with neglect of psychological factors in disease, the usual defence mechanism of the clinical scientist is strangely and illogically three-phased: "In psychological medicine there is no corpus of proved knowledge to teach ; if there is, there is no way of teaching it ; in any case, I teach and practise it myself." Believe me, I am not describing something out of my distant student days, but recounting, without exaggeration, facts and opinions which have come to me through personal contacts during the last two years.

And yet the extent to which the mind and personality influence all illness must be obvious to any who do not close their eyes to the realities around them. One has only to observe two diabetics, for instance, scientifically indistinguishable, both requiring diet and insulin, to see how one will retreat into neurotic invalidism, abetted by his wife in the building of an elaborate and protective ritual, while the other regards his daily life as almost uninfluenced by a few minor inconveniences.

Of course clinical teachers vary greatly in their approach to these problems, and psychiatrists vary too in the amount of help and collaboration they are prepared or, let us admit, equipped to give ; but even those who, like myself, have always delighted in the study of people do not, I think, sufficiently realize the amount of our neglect and the full extent of our conformity—"so much doth wont and custom become a second nature"—for we have not asked ourselves the essentially Darwinian-cum-Freudian question—to what end and for what purpose and in response to what selective pressures have the teaching hospitals evolved in this way ?

From a research point of view, the defence which requires most serious thought is that "the time is not yet ripe for serious research into psychological medicine. Like infective disease before Pasteur, it awaits a break-through in knowledge." This view, which is rather a favourite at the present time, seems to me quite untenable today. The nature of infectious disease before Pasteur was quite unknown. Though the causes of psychological illness are multiple, varied, and infinitely complex, no one doubts that they are to be found in interactions between heredity, emotional development, social, environmental, and cultural influences, chemical changes (including drug action), and organic cerebral disease. Every one of these can be studied today by methods far more rigorous than existed even a few years ago. Indeed, they are being studied already to great advantage.

## New Approaches

Important in this is the study of symptoms revealed by the psychiatric interview aided by modern knowledge of observer error and computer techniques of information storage and analysis, and the validation of methods and conclusions. There

is room for new approaches to the study of human behaviour in health and disease, on the lines of Tinbergen, Lorenz, and Desmond Morris.

"The central features of scientific method," says Martin Roth (1967), "are the dispassionate observation, recording and analysis of data aimed at deriving reliable answers to clearly formulated theoretical and practical questions. The advantages of quantification and controlled experiment are undeniable. But they may be inappropriate or applicable only to a limited extent at certain stages in the development of systematic inquiries in some fields of knowledge. This need not disqualify a discipline from scientific status, provided that the essential criterion, the unbiased collection and verification of observations can be satisfied."

Or, as Gaylord Simpson (1963) has said, the multiplication of relevant observations will not prove a hypothesis, but the more that they fail to disprove it the more confidence we have in the hypothesis ; but the proviso is that the observations must be relevant, and to be relevant they must be capable of disproving the hypothesis. These surely were the methods of Darwin, of which we have no need to be ashamed.

There is enough in psychological medicine to keep an army of research workers fully employed for many years, but we shall not attract enough of the right men and women into the study of the mind if we continue to give medical students in their early and formative years no contact with man except as a corpse or a machine, and continue to build up elaborate defences between ourselves and the minds of our patients.

Should anyone doubt whether human behaviour is a fit subject for study, let him make observations on his colleagues, especially in committee. He will soon find behaviour patterns as specific as the song of the thrush ; and let him inject noxious stimuli in the form of unwelcome concepts from time to time, and he will find that defence mechanisms springing direct from the unconscious, uninhibited by the rules of logic, surface promptly to the appropriate summons. But perhaps I have been overzealous in what probably amounts, for me, to replacement therapy in my period of bereavement for the loss of clinical medicine, my constant companion for about 45 years, and I had better turn rather hastily to my last subject.

## Medicine versus Science

The real distinction between medicine and science is not, of course, a matter of method, nor is it the recognition that man is something more than a machine. It is a matter of aims. The object of the true scientist is discovery ; the object of the doctor is to plan the method of action judged to be of best value to the individual. That the aims are different is undeniable ; fortunately they do not have to be invariably in conflict.

The first need of the doctor is to have knowledge of the human body and mind in health and disease. Clinical science in medical departments has contributed greatly to knowledge of the body and almost not at all to knowledge of the mind. Given that he has this basic knowledge, the doctor's next task is to find the facts and to evaluate the clinical situation as it develops from day to day throughout the illness. In this he has science and technology among his tools, and he must know how to use them, but he will often find that the evaluation and judgment of the human mind far outweigh the value and accuracy of scientific measurement ; and, of course, he requires other qualities, of understanding, insight, interpretation, compassion, and a carefully practised technique, without which the very facts on which he can base a reasoned plan of action will elude him, for they will not cross the barrier between him and the patient's mind. There is, of course, nothing which denies the clinical scientist of these qualities.

In the enthusiasm for teaching principles, the fact that much of medicine depends on the acquisition of technique is sometimes overlooked. Technique can be crucial where academic knowledge is useless. I wonder if Paganini ever realized that he was playing on a logarithmic scale ; or cared.

To use the new aids which science has now put at his command the doctor does not have to know the scientific principles from which they have developed ; and as science advances and becomes more complex it becomes increasingly impossible for him to do so. This should be accepted by medical educators without guilt or shame. The modern physician does not have to learn the engineering and physical principles on which an *x*-ray machine is constructed or the chemical nature of the emulsions used on the film in order to interpret an *x*-ray picture. (Even the interpretation is usually done for him.) He does not have to be a physicist to read an electrocardiogram. Almost none of the physicians who daily prescribe the tetracycline group of drugs knows anything about their chemical structure ; or cares. Science is throughout the servant, not the master, a servant to be used with understanding and called on unsparingly in the patient's interest, but dismissed peremptorily and without remorse on all those many occasions when the patient is better off without its services ; not only when science becomes a mere intruder in private affairs, but when it has led only to false clues, and the imperative need is to go back to the intimate confrontation of the patient for the information which he alone can give.

This should not mean that the doctor is disinterested in discovery, in the use of new remedies, or in the proper scientific appraisal of all that he does. Indeed, he should welcome the opportunities which scientific medicine presents in these respects ; but I believe it to be more difficult to teach the true aims and values of the practice of medicine to undergraduate students from a department in which the primary aim is too obviously research and discovery, in which science has become the master. I know that there will be many who do not agree with me and who see no conflict and no antithesis between the aim of the good doctor and that of the good scientist. They will make the point that when a patient is seriously ill his foremost need is to be under the care of whoever has most knowledge of his kind of illness. This ingenuous view, which at first seems self evident, implies that someone else has first selected the right patient for the right department, and, secondly, that the illness is amenable to treatment or relief by modern medical science and not solely to diagnosis and investigation. "Guérir quelquefois, soulager souvent, mais rechercher toujours."

What is, of course, true is that the same man may wear the mantle of the doctor or that of the scientist with equal grace at different times and occasionally at the same time. Nevertheless, I think that this does not come easily to all people at all times, and such evidence as we have from John Aubrey and Lord Conway and other sources strongly suggests that Harvey himself found the compromise a difficult one. Lord Conway's letter of 1651 to his daughter, who was Harvey's patient, says: "I heare that you have a great opinion of Doctor Harvey. I thinke you doe well to love and respect a person of his merite for I thinke he hath deserved extremely well of all learned men for what he hath found out . . . but in the practice of Physicke I conceive him to be to mutch governed by his Phantasy . . . . To have a Physician abound in phantasie is a perilous thing. . . ."

## Conclusions

You will see, Mr. President, that I think the clinical scientist has certain difficulties which do not present themselves to the non-clinical scientist in medical research. I also believe that clinical science in its present state of development has neglected some of its opportunities, and has shown an unfortunate tendency to follow only the methods of physical science, which try to prove everything by contrived experiment, to the neglect of discovery by deliberate and relevant observation and the kind

of evolutionary—or, if you like, teleological—thinking so necessary to the study of biology. For in biology, because of Darwinian selection, we are entitled to ask not only "What ?" and "How ?" as in physical science, but also "Why ?" and "What for ?"

Because in clinical science we pride ourselves that we are building up medical knowledge we should not complacently assume that we are always doing it the right way, or making the best use of resources which in any society are bound to be limited. We should remember with John Aubrey that "Pride has been one of the greatest stoppers of the Advancement of Learning."

The defects may be only part of a temporary chapter in the history of medicine, and a symptom of a more widespread ailment. For man has put most of his efforts into improving the material state of society (and perfecting the engines of war), and has given scant attention to the ills of the mind of man and woman, and the study of their behaviour in health and disease and in society.

I know that I have spoken some heresies. If they are rather disturbing ones, my personal researches lead me to believe that the defences of the clinical scientists will be equal to them. Perhaps for another few years.

Nevertheless, with Harvey, "I fear lest I have mankind at large" (or at any rate some of my colleagues) "for my enemies, so much doth wont and custom become a second nature. Doctrine once sown strikes deep its root . . . . Still the die is cast and my trust is in the love of truth and the candour of cultivated minds."

REFERENCES

Chain, E. B. (1963). *Nature (Lond.)*, **200**, 441.
Clark, Sir George (1964). *A History of the Royal College of Physicians of London*, vol. 1. Oxford.
Jason, H. (1966). *J. Amer. med. Ass.*, **198**, 199.
Keynes, Sir Geoffrey (1958). *Harveian Oration to the Royal College of Physicians*. London.
—— (1966). *The Life of William Harvey*. Oxford.
Medawar, Sir Peter (1967). *The Listener*, **78**, 453. (12 October.) And see also *The Art of the Soluble*. London. 1967.
Pappworth, M. H. (1967). *Human Guinea-Pigs*. London.
Roth, M. (1967). Unpublished.
Rutstein, D. D. (1967). *The Coming Revolution in Medicine*. Cambridge, Mass.
Simpson, G. G. (1963). *Science*, **139**, 81.
Thomson, Sir Arthur (1961). *Brit. med. J.*, **2**, 1303.
Whitteridge, G. (1964). *The Anatomical Lectures of William Harvey*. Edinburgh.
—— (1966). *Brit. med. J.*, **2**, 7.

# Factors Affecting the Response to Clomiphene Therapy

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It has been well established that clomiphene citrate (Clomid), a compound allied to chlorotrianisene (Tace), is capable of inducing ovulation in a substantial proportion of patients suffering from anovulatory infertility, with consequent relief of infertility in a significant number. In the present study we attempt to determine factors concerned with the outcome of such therapy.

## Material and Methods

Fifty-five patients attending one gynaecological and one endocrine clinic with amenorrhoea, severe oligomenorrhoea, or mild oligomenorrhoea with anovulatory cycles have been treated with clomiphene. Forty-one of them were also suffering from infertility or amenorrhoea of more than two years' duration. All the patients had a full medical and gynaecological examination to exclude medical or gross gynaecological disorders likely to be associated with menstrual disturbance or infertility. All kept a basal temperature chart for at least six months, often much longer, before treatment, and continued to do this throughout therapy. Gynaecography was performed in 51. In those with infertility endometrial curettage and culture for *Mycobacterium tuberculosis*, hysterosalpingography, and analysis of the husbands' seminal fluid was carried out. Follicle-stimulating hormone assays were not done, but primary ovarian disorder is thought to have been unlikely on clinical grounds.

Oestrogen excretion assays were carried out on 39 patients, both under basal conditions and after treatment with clomiphene. At first, assays were done at weekly intervals for one month after the start of treatment; experience showed that oestrogen responses tended to be maximal between the second and third weeks, and in the later stages of the investigations assays were performed only on specimens obtained during this period. Total oestrogen assays were made with a modified form of Ittrich's method (Corns and James, 1967), which had a non-specific fluorescent background of 10 $\mu$g./24 hours.

Various dosage schedules have been used, ranging from 50 mg. b.d. for five days to 100 mg. b.d. for two weeks. No obvious advantages were found for the longer schedules, and eventually a standard dosage of 100 mg. b.d. for five days was used. All patients were given at least three courses of treatment before it was concluded that no benefit was to be obtained.

## Results

*Criteria Used in Evaluation of Results.*—Three types of response to clomiphene were distinguished: (1) no response, (2) menstruation without ovulation (as evidenced by absence of progestational temperature rises), and (3) ovulation and menstruation. Examination of our data suggested that the most meaningful classification would be into those with and those without evidence of ovulation. The criterion used for the diagnosis of polycystic ovaries was a gynaecography index exceeding 21 (Ferriman and Purdie, 1965).

*Ovulatory Response in Relation to Duration of Cycles.*—Consideration of our findings suggested that a significant division would be into patients with menstrual cycles less than or exceeding six months. The data have been analysed accordingly and the results are shown in Table I. Clearly patients with cycles of less than six months' duration fared better than those with cycles exceeding this figure. The difference is highly significant at the 0.1% level ($\chi^2 = 12.40$).

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