The Evolution of Therapeutics: Osler’s Therapeutic Nihilism and the Changing Pharmacopoeia.

The Osler Oration, 1978

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Those who have read or written an obituary of a friend will know how, in the end, the personality of the man himself seems to slip through one’s fingers. Although I used Osler’s textbook as a student, have had the Bibliotheca Osleriana for over 30 years, and spent my preclinical years at Oxford with its Osler tradition and its undergraduate Osler Society, yet, in my recent reading about Osler, I found the same elusiveness. There is much written about him, and it is written with authority and affection: for instance, Cushing’s major biography (1925); the Memorial Volume, amplified in its second impression and containing Osler’s own bibliography (Abbott, 1927); the admirable entry by A. E. Garrod in the Dictionary of National Biography; the portrayal of the Radcliffe Infirmary in Osler’s day by Robb-Smith (1970); and most recently, papers about him collected and printed by the Osler Club of London in 1976 (Franklin, 1976), celebrating their 300th Meeting the year before. In preparing this lecture, it was Dr Newman’s paper in the last-named, on ‘Osler as a Physician’, that, brief as it is, was particularly liberating. This was partly because of the unrelenting eulogy of earlier writing, though Johnson did say that, in respect of ‘lapidary inscription a man is not on oath’. But affection and admiration do not prevent Dr Newman (nor the other contributors) from showing that he was, after all, human.

I must stress that any assessment of mine of Osler’s achievement is far too uninformed to matter—except as it bears on my own argument. In this I want first to consider Osler’s reputed therapeutic nihilism, together with suggesting something of its roots and noting the extent to which it was shared by others. Then I will review the development of the pharmacopoeias—one objective way of getting some mental leverage on the shaping of therapeutic practice—so as to provide a broader context. From that emerges, I believe, first a picture in which pharmacology and therapeutics showed a remarkable delay in development, then a burst of growth, and finally, recently, some recession. In considering reasons for all this I will come nearer my title, which arises from a remark by Lord Platt (1967), who asked for what purpose and in response to what selective pressures had the voluntary hospitals evolved as they did. This dynamic approach suggested an attempt to see what forces were at work shaping therapeutics and pharmacology over the years, and what forces there may be still to come.

So, in taking Osler and his own therapeutic approach as a starting point, I needed first to get some more solid view of him, to assess, as it were, the nature of the authority that lay behind his opinions.

There must have been many factors in his achievement and resulting dominance. The important one, it appears to me, is that he seems early to have placed himself firmly in, and indeed to have created, one of those dramatic fruitful successions of teachers and taught that one associates also with other names like Thomas Lewis, Sherrington, Dale, Rutherford, or the Cambridge school of physiology. This is the same point that Dr White Franklin made in the second Osler Lecture, taking up Osler’s own categories of creator, transmuter and transmitter, and showing Osler as ‘a transmuter’ of the humanist tradition. Osler was himself devoted to three teachers: the schoolmaster-parson W. A. Johnson, with his microscopes; James Bovell, professor in Natural Theology—which meant physiology and pathology—at Trinity College, Toronto; and R. Palmer Howard, Professor of Medicine at McGill. Then, in turn, aided by a prodigious memory and a prodigious power of retrieval from it, he poured out his vast clinical experience (transforming methods of medical education in the process), his stock of literary allusion, his joking and teasing, his knowledge of bibliography and history of medicine, to those who would take them. Some people, doubtless, at heart preferred a more equal mutual stance, or perhaps liked not to be helped quite so much. Then, too, no man can do everything, so some aspects of science are scantily represented. Some might feel that in his therapeutic garden (until joined by Macrae around 1900) he pruned more than he grew. One could disagree with some of his judgements. Yet it remains clear that he had what can only be called a genius, with something creative in it, in a particular type of invigorating friendship, to which he brought kindness, generosity, unstinting energy and affection. But none of these phrases, two or three generations later, at second or third hand or worse, are satisfactory: and my own image of Osler mostly rests now, not on the record of a dominating medical, literary, bibliographical figure, ‘the one man’ (as Pearson wrote to Francis Galton in 1908) ‘before whom all medicine bows...
down', but on five photographs: the thoughtful child, sixth son of a missionary in the Ontario backwoods; the pathologist intently dissecting; the writer, hammer-and-tongs among his piles of references; the physician at the bedside, not talking, demonstrating or showing off, but looking and thinking; and lastly, the Regius Professor at Oxford, intent on boosting an undergraduate's morale (Figs 1–5). Osler loved the young of all ages. The death of his only son in 1917 shattered him. Cushing's phrase, with which he ends his biography, about the men in that war who died twice 'because they died so young' is surely one that Osler would have echoed. There was an old country-woman who 'did not know what she thought till

Figure 1. Family group showing Osler (W. O.) as a child of seven. Next to him are three brothers, Francis (9), Edmund (11) and Edward (14), then Nellie (15) and Charlotte (9). The other five figures are their neighbours the Gavillers. (From International Association of Medical Museums Bulletin No. IX. Sir William Osler Memorial Number, Montreal, 1926).

Figure 2. Osler at the Blockley mortuary (Philadelphia Hospital) about 1886. (From Memorial Number, 1926.)

Figure 3. Osler writing the Practice of Medicine. Johns Hopkins Hospital, 1891. (From Memorial Number, 1926.)

Figure 4. Osler and the patient, Johns Hopkins Hospital (From Memorial Number, 1926.)
Then, in a later lecture recalling the past, cited in Cushing (II, 180):

'Upon us, whose work lay in the last quarter of the nineteenth century, fell the great struggle with that many-headed monster Polypharmacy—not the true polypharmacy which is the skilful combination of remedies, but the giving of many—the practice of discharging a heavily-loaded prescription at every malady, or at every symptom of it. Much has been done and an extraordinary change has come over the profession, but it has not been a fight to the finish. Many were lukewarm; others found it difficult to speak without giving offence in quarters where on other grounds respect and esteem were due. As an enemy to indiscriminate drugging, I have often been branded as a therapeutic nihilist... I bore this reproach cheerfully, coming, as I knew it did, from men who did not appreciate the difference between the giving of medicine and the treatment of disease.'

All this reflects simply a frank recognition, doubtless overdue, that most of the drugs then used were in fact ineffective. That does not mean that he was backward with effective drugs. The following, from Allbutt's *Arteriosclerosis* (1925), dealing with the treatment of 'hyperpiesia' by vasodilators, is probably typical:

'At times of crisis Sir W. Osler and others have pressed up the nitrates to huge doses, in persons upon which these drugs had been well tested. Sir William said he had never seen harm come of large doses if cautiously approached. I think he used to speak of 20-30 grains of sodium nitrite per diem. I have administered half as much in a day.' (pp 88-9).

But in addition to a scepticism suitably tempered on the right occasion, there are two other notes sounded. First, this (Cushing II, 179):

'To accept a great group of maladies, against which we have never had and can scarcely hope to have curative measures, makes some men as sensitive as though we were ourselves responsible for their existence. These very cases are "rocks of offence" to many good fellows whose moral decline dates from the rash promise to cure. We work by wit and not by witchcraft, and while these patients have our tenderest care, and we must do what is best for the relief of their sufferings, we should not bring the art of medicine into disrepute by quack-like promises to heal, or by wire-drawn attempts to cure in what old Burton calls "continue and inexorable maladies".'

For someone passionately interested in morbid anatomy, and with the appallingly advanced pathology he would have seen at autopsy, it could well have seemed unrealistic to suppose that such changes could be prevented or cured by giving yet other chemical substances, when those in use were so ineffective. He must, also, have found pathology intellectually far more satisfying than therapeutics as he saw it practised: witness, for instance, his praise of Virchow, 'father of modern pathology', where he contrasts 'pills and potions', on the one hand, with 'the gains of science' that Virchow's
work brought, on the other (Cushing I, 355). Perhaps, too, Burton's phrase 'continue and inexorable maladies' held a deep, almost romantic, attraction—a hinting at other approaches, faith and courage in the face of inexorable fate. This comes out in another extract from 1901 (Cushing I, 546):

'A third noteworthy feature in modern treatment has been a return to psychological methods of care, in which faith in something is suggested to the patient. After all, faith is the great lever of life. Without it man can do nothing; with it, even with a fragment, as a grain of mustard-seed, all things are possible to him. Faith in us, faith in our drugs and methods, is the great stock-in-trade of our profession. In one pan of the balance, put the pharmacopoeias of the world, all the editions from Dioscorides to the last issue of the United States Dispensatory; heap them all on the scales as did Euripides his books in the celebrated contest in The Frogs; in the other put the simple faith with which from the days of the Pharaoths until now the children of men have swallowed the mixtures these works describe, and the bulky tomes will kick the beam.'

Perhaps one can summarise all this: a deep scepticism about current remedies; a determination, with those that did work, to use them really effectively; a dissatisfaction with the depth of their scientific study hitherto; an ultimate lack of interest in the mechanisms of their action, compared with the entrancing studies of aetiology and pathology; a doubt whether many diseases were curable anyway; and a physician's instinct to deal with a patient in his wholeness. One may call it therapeutic nihilism, though scepticism would be a better term; but it is not a discreditable attitude.

I think, too, we can see influences that would push Osler in this direction. To quote two small lines of evidence. First, Osler lived from 1849 to 1919. It is striking that the table in Singer and Underwood's History (1926, p. 391), showing the dates of discovery of the principal micro-organisms, spans almost exactly his lifetime—from the discovery of the anthrax bacillus in 1849 to Haemophilus pertussis in 1906 and bacteriophagew in 1915-17. To anyone living through this period, bacteriology and pathology must have seemed obviously the winning lines. Second, Osler came under Sydney Ringer's influence. Speaking of his time at University College London in Burdon Sanderson's laboratory, he mentions how he 'learned from Ringer, Bastian and Tilbury Fox how attractive out-patient teaching could be. Ringer I always felt missed his generation, and suffered from living in advance of it.' Then on his second visit to England he records that he 'rarely missed a visit with Bastian and Ringer'.

If you now turn to Ringer's Handbook of Therapeutics (1869), which, presumably, expresses what he taught, one gets something of a shock. The first pages deal successively with oxygen (1 page), the internal use of water (3½ pp), cold (20 pp), ice (2 pp), and warm and hot baths (3 pp). We then work through the elements and inorganic compounds, and do not really come to a specific remedy until ipecacuanha on p. 293. At the end is an index of diseases, with appropriate remedies, e.g.:

for cholera, arsenic or camphor; for diabetes, oxygen, bromides, acids or alkalis; for meningitis, ice; for puerperal fever, turpentine. The point I wish to make is not the oddity of some of these remedies to our eyes now—that takes no account of the knowledge available at the time—but the sparseness of them. Vastly many more drugs were in fact being prescribed; but here was the first professor of therapeutics in Britain deleting almost all of them, in favour usually of physical methods or the simplest inorganic ions.

Was Osler unusual in this therapeutic scepticism? It is clear that others shared his views, well illustrated by Abraham Flexner in his 1912 report, Medical Education in Europe: he wrote as follows:

'While miscellaneous dosing was still generally prevalent, intelligent practitioners had been infected with nihilistic doubts from two highly divergent sources: the disclosures of the autopsy table brought an overwhelming conviction of the futility of elixirs and extracts to combat, to terminate, or to repair organic changes so profound and destructive; homeopathy, by appearing to demonstrate that minimal are as effective as larger doses, hinted at the perhaps frequent impotency of both. The immediate outcome of the nihilistic mood was a wholesome emphasis on physiological therapy. We are apparently—so the argument ran on—powerless to cure; but a rational mode of living, in the first place, prevents disease, and, in the second, assists the body struggling for survival to regain its normal course.'

That might have been written by Osler, although, in fact, Osler's initial reception of the report was, for quite other reasons, very critical (Cushing II, 292-3). Flexner, however, does not stop on this rather pessimistic note, but takes up some optimistic features in recent developments in German pharmacology:

'The new science of pharmacology represented from the start a distinctly more hopeful therapeutic attitude; instead of discarding, it undertook to probe; not content with testing traditional and empirical claims, it ventured the effort to ascertain the physiological effect of drugs hitherto unemployed. Finally, proposing to itself definite clinical and theoretical problems, it sought to create agents capable of coping with them. Its most recent outcome, Ehrlich's salvarsan, is a deliberate effort in constructive therapy.' (Flexner, 1912, p. 88).

Flexner saw some other important points. Thus:

'Pharmacology is indeed capable of a pure development; that is, given drugs and animals, an indefinite investigative evolution is possible. In its course practical results will undoubtedly emerge, the more surely, perhaps, if they are not too eagerly desired or too narrowly pursued. Meanwhile the science would cut itself off from a fertile source of suggestion if it lost touch with the clinic.'

And later:

'Only where pharmacology attains the status of a
university department do productive workers follow one achievement with another.' (p. 127).

Had Flexner now moved ahead of Osler? It is interesting to see what follows later, when he outlines the state of pharmacology and therapeutics in England:

'As late as 1906, the provision for pharmacology at Oxford was described as "little better than a shed". The lecturer's only assistant was a boy who swept out the room. All the mechanical work was done by the lecturer. A great part of the apparatus belonged to him, and there was no convenient place to lodge it in safety where his lectures were given. In most schools the instruction is assigned to physicians not otherwise engaged. At Guy's an assistant physician lectures; the demonstration classes are held by a teacher who also does duty in two other departments—physiology and forensic medicine; at the London, there are two lecturers, a physician and his assistant physician, the latter conducting the demonstration and quiz classes; at Charing Cross, an assistant physician gives all instruction in materia medica, pharmacology and therapeutics; at the Middlesex, the same function falls to the physician to the outpatients department; at Sheffield, where I was informed that "small schools cannot afford pharmacology", one of the physicians to the Royal Infirmary is also medical officer to the skin department, and professor of all three branches under discussion (i.e. anatomy and physiology too).'(p. 128)

The report of the state of affairs at Oxford was in fact based on an anonymous article by Osler in 1906, on his arrival at Oxford as Regius. This article added: 'It is a disgrace that a great University like Oxford should be without a properly equipped department of pharmacology."

These were not mere words. In 1912 (Cushing II, 338) such a department was created, opening on 9th November with an address by my predecessor but one, J. A. Gunn, and a historical speech by Osler. Characteristically, he reminded the Vice-Chancellor (who was Principal of Brasenose) that Withering's monograph on the use of digitalis was inspired by the results of its use on a previous holder of his office, and while tea was served, editions of Dioscorides were displayed! While I think Osler never got fired by therapeutics, as he had been by clinical medicine and pathology, and he shows no appreciation of the importance of chemistry for pharmacology (a point Flexner grasped), yet one admires and is very grateful to a man who could move from such scepticism to such support.

Let me have one last extract from Flexner, still relevant today, when writing on hospital building in England's medical schools:

'While weak in medical equipment, I hasten to add that whatever devices tangibly contribute, or are credibly supposed to contribute, to direct therapeutics, the voluntary hospitals introduce as rapidly as their financial resources allow. For the care of patients they are therefore equipped in a progressive spirit. Great emulation is displayed in this matter: the various institutions vie with one another in operating-room installations, X-ray plants, coloured-light baths, etc. But back of these improvements lies largely only the practical, empirically assimilative spirit: the critical, aggressive inquiring initiative that itself invents and discovers may and does crop out in individuals, but is not reckoned with in the structure and equipment of the hospitals themselves."

Flexner then quotes Osler: "Hospitals have been built by men who had no idea whatever of their scientific needs" says Professor Osler' (p. 197).

The Evolution of the Pharmacopoeia

It is not easy to obtain a comprehensive view of the way pharmacology and therapeutics have developed. Particular instances, or particular reminiscences, are bound to be selective, leaving it quite uncertain how generally they apply, and whether they overstate or understate a general case. One approach is to look at the development of the pharmacopoeias. These do not, of course, represent all the medicaments used in practice. There is a sort of gradation of holiness: there is the whole body of drugs believed by somebody to be of virtue, on or off prescription, subject to the limits of the Poisons Regulations, that are used to treat disease; then there is the more blessed group of substances which have received an Approved Name from the British Pharmacopoeia Commission; and finally those canonised by inclusion in the British Pharmacopoeia. The last-named—because it is carefully reviewed in full by a considerable range of responsible and knowledgeable people every five years—gives the best continuing picture of the backbone of therapeutics, and in a manageable compass. Some years ago (Paton, 1963) I attempted some analysis of these pharmacopoeias, initially to seek an answer to a particular historical question. This was as follows. Pharmacology and therapeutics show a remarkable lag in development. There had been successful analyses of the mechanisms of drug action from 1809 onwards. Structure-activity studies have been initiated in 1868, and an astonishingly modern study of drug antagonism between 1850 and 1870. There had been several demonstrations of how to discover or synthesise and introduce a new drug. Yet, even such a book as Binz's excellent textbook of pharmacology (translated for the New Sydenham Society in 1895), contained hardly more than a handful of significant remedies for general practice beyond those to be found in (for instance) John Ayerton Paris's Pharmacologia of nearly a century earlier. In a way, one is here merely re-echoing Osler's response to the state of therapeutics as he found it. But having noted this, one wondered what it was fair to expect: what is 'fast' in the progress of a science? So I turned to the pharmacopoeias to see if one could get some light on this over the centuries. Figure 6 shows what first emerged. For it, I accepted what seemed to me a reasonable continuity between the old College Pharmacopoeias and the first British Pharmacopoeia of 1864, and it is likely that a similar group compiled each, so I have not distinguished them.

The first stage is the pruning of the Galenicals. The huge first College pharmacopoeia contained nearly 2,000
items. Most of them were probably innocuous, some record-breaking in the number of their constituents, such as the Theriaca Andromachi and the 'ton-up' Antidotus Matthioli. But by 1746, in the College's pharmacopoeia translated by Henry Pemberton (editor of the third edition of Newton's Principia, Professor of Physic at Gresham College, FRS and amateur mathematician) there were only about 650 items (Dispensatory, 1746). Along with the thinning in numbers, an immense reduction in the complexity of the preparations was achieved. The next stage was what I take to be the first steps towards pure active principles, namely the rise of the tincture and of the extract, each seeking to separate out the active principles according to physical properties — fat-soluble or water-soluble. This phase, whose beginnings go back a very long way, lasted up until the 1930s.

Knowledge of microbial infection and of methods of disinfection, together with the introduction of the hypodermic syringe, made hypodermic injections possible in the latter part of the nineteenth century; but injections did not 'take off' until the period of the pure active substance began in the 1930s. Along with this went the growth of tablets. This was catalysed by Henry Wellcome's insight into the virtues of a convenient form of medication of constant stable composition; the word 'Tabloid', which he patented, introduced a new word into the English language. With these developments, the age of the tincture declines.

Two new features also appear around now (Fig. 7). The first, from 1932, is the use of biological assay, to standardise those substances that still baffled the skill of the chemist. Fifteen years ago, I thought these were levelling off. In fact, the need for biological assay has increased since then. It is an interesting feature of medical research that our knowledge that substances have an important pharmacological effect can still run ahead of our knowledge of their exact constitution; activity can still run ahead of structure.

The other feature is the growth in application of synthetic chemistry. It is not easy to estimate this; but the line I have drawn counts drugs not derived from natural sources (beginning with ether and chloroform), and usually wholly synthetic in origin. Each such structure can give rise to several preparations, so that their number by no means reflects the extent to which the pharmacopoeia is now synthetic.

Finally, one can now attempt some estimate of rates of change. Two fairly accessible indicators suggest themselves. The first is the number of compounds each year receiving an approved name (the 'blessed'). Only a proportion of these — around 1 in 6 — ultimately get as far as the British Pharmacopoeia (the 'saints'), so that they represent a measure of change partially independent of the latter. The system did not start until 1948, so it gives us a view only after the therapeutic burst had begun; but it can be assessed annually, covers an important period,
Figure 8. The rise, levelling off, and fall in the number of Approved Names published by the British Pharmacopoeia Commission from 1948 onwards.

and still continues. Figure 8 shows the annual figures. In 1963, when I first analysed the data, we were in a period of accelerating growth. But it was in that year that the Safety of Drugs Committee was set up in response to the thalidomide tragedy two years earlier. The intervening 15 years have seen a levelling off in new names, and then a fall, after a short latent period when (one supposes) drugs already in the pipe-line and nearly processed went through. Perhaps there is some sign of growth again.

The other measure is with the pharmacopoeia itself. As a simple index, I have used the number of preparations added to the BP at each review, expressed as a percentage of its size, and divided by the number of years since the last revision. As well as additions there are deletions, so that there is a sort of partial rinsing of the pharmacopoeia that has allowed a slow growth in total size since the initial pruning. One can think of more elaborate analyses, with ratios of influx and efflux, or perhaps a coefficient of permeability of the Commission to new products. But for the present purpose, the rate of acceptance of innovation, measured by proportionate annual influx, seems sufficient. Figure 9 shows the outcome. After the long flat period up to the 1930s comes accelerating growth up to 1963, with a clear decline subsequently. The present level is a little over a third of the peak, and corresponds roughly to the level of 25 to 30 years ago. Here is the pharmacopoeial impact of the process Professor Dollery described in his recent Rock Carling lecture entitled 'The End of an Age of Optimism.'

We can see, in this hundred-year view, that the rates of accepted therapeutic innovation stay almost constant at a low level for many decades, rise to between 10 and 15 times the 1883 level, and then fall back. This rate really was rather slow in the latter decades of the last and early decades of this century. For the pharmacologist, too, recalling what the fundamental ideas needed, namely structure-activity study, drug antagonism, the analysis of mechanism of action, methods of isolation or of chemical synthesis, and the technique of moving from test-tube to animal test to clinical trial, had all been developed and illustrated by 1890, it is strange that we had to wait 40 years for the major dividend. There are several possible reasons, but the more I appreciate the depth of Osler's interest in pathology, and the influence he had, the more I think one of the prices that had to be paid for that interest, by him and others, was a holding back of the therapeutic impulse. One cannot regret the growth of pathology, but I do think it reflects the permanent danger of over-enthusiasm and over-investment in one area of medicine.

This brings me nearer to my evolutionary title. We have seen something of the rise, and partial fall, of a species of activity that I believe to be beneficial, to have survival value, namely the impulse to therapeutic innovation. What selective pressures have shaped that pattern? One I have just suggested: a competition from another impulse of great power, the impulse to distinguish disease processes—to name them accurately, to describe them more deeply, and to predict their outcome more exactly. Then again, the idea that disease should be combatted may be questioned, and the virtues of suffering praised. But every time I hear Illyich's name, or hear the topic mooted by a sufficiently-nourished middle-class intellectual, I think of Cold Comfort Farm, (Gibbons, 1958): 'We are purified by suffering' said Claud, helping himself to more crab. If one looks around and reflects on life, there seem ample reserves of physical and psychic damage and little risk that the scope for such self-purification will soon (or ever) be diminished. Against all this the therapeutic impulse is stimulated by each new success, by each occasion when the still unsolved diseases are vividly presented, by patient demand (though this may seek to push at doors not ready for opening), by the industrial search for profit (that currently despised activity to which is so largely due the widespread availability of medical advance), and by new discovery in other fields. Success feeds on itself, and one hardly needs to look further for the burst of growth from the 1930s.

But there are some important predators on this potentially flourishing intellectual species. One is the
assertion (by no means a new one), based almost wholly on mortality data, that the successes of therapeutics have been far less than its champions claim; a greater success being attributable to improvements in nutrition, hygiene, or other influences. In an ideal world, with ample resources, there would be little to argue about; no one would reject one benefit because it was less than some other. But that is not the position; and if resources are scarce, then the cutting edge of a decision as to the best way to distribute those resources comes into play. This is undoubtedly relevant to the aims of pharmacology and therapeutics. First, consider the procedure of expressing the fall in mortality since the introduction of some therapy as a proportion of the total fall since some earlier date: it is suggested, for instance (McKeown, 1976) that chemotherapy has been responsible only for 3.2 per cent of the fall in death-rate from tuberculosis between 1848 and 1971. What is the point of this? One could, by judicious choice of the earlier date, reduce or magnify the significance of any later development. Why not go back to the Breslau data of the seventeenth century, with an expectation of life of 10 years, and show how over-estimated has been the work of Chadwick? Nor is it obvious what the appropriate deduction is from such an approach. If one believes one has shown some dramatic effect of, say, hygiene, might this not mean that this weapon is nearly exhausted and we must now turn elsewhere? It would be more relevant, if one wished to make these extrapolations, to consider trends as they were just before some measure was introduced—a non-arbitrary starting-point—and to include an estimate of the error attached to those trend-lines. But in any case, how sensitive is mortality as an index? For instance, suppose one could prolong the expectation of life in sufferers from some chronic disease by a median of 5 years, and that this benefit was (as is likely) gradually introduced. What statistical effects would one expect to see? First, an increase in the number suffering from the disease (since they survive longer); second, an increase in deaths from other diseases (which must be expected to exact some toll from these extra survivors); and, third, a very blurred fall in the mortality rate, which should persist if expressed as a proportion of those with the disease, but if expressed in absolute numbers or as a proportion of the total population would rise again with the growth of the pool of survivors. It seems to me very uncertain indeed whether so substantial a benefit would be detected by present techniques.

The second obvious point is that morbidity is becoming increasingly important as diminishing returns operate in reduction in mortality and lengthening of expectation of life. But how does one trade off so-called 'quality of life' against duration of life? Until some valid approach to this has been found, a vital part of the basis for any decision-making is missing.

The third point is to avoid setting medicine at odds within itself. In any case, epidemiology, nutrition, hygiene, therapy, all interact and help each other. For instance, therapeutics raises standards of living; and, in turn, as John Waterlow has shown, a well-nourished body responds better to therapy. But there is a more important point for the therapeutic scientist. The full assessment of the value of some treatment is not easy. We know, in principle, how to establish mechanism of action, to work out what a drug ought to be capable of doing in practice—that is a biological problem. We now know how to try it out on selected groups of patients—the clinical trial—although the sensitivity of such trials (i.e. the size of a benefit that might be real but would not be recognised) is not always explained. If one could finally go further, and use valid measures of morbidity as well as of mortality, of known precision, that would provide a really valuable final test at the population level. In the end, this approach should not be resisted, but itself used to improve therapeutic result. Insofar as there is any implied suggestion of establishing priorities in methods of study, this seems to me a kiss of death. The only safe line is to accept all lines of investigation in principle, and to retain a flexibility that allows resources to go (in the old MRC phrase) to enterprises of timeliness and promise. If the flow of new ideas begins to fade—that would be the time to divert resources.

The second great and insidious predator is impatience. My image for this is that student's favourite, the fish tapeworm Diphyllolothrium latum, doubtless a harmless lovable creature in many ways, save for its consumption of the vitamin B12 one needs for oneself, so that gradually a pernicious anaemia is produced. So, too, does the taking of short-term views about the research needed to advance therapy gradually starve the therapeutic impulse of its essential scientific vitamins. How can I illustrate this old point about the long, unpredictable lead time from academic study to development? I remember, in my laboratory at the College of Surgeons housed in the Examination Hall in Queen Square, each year there was a visit from the Conjoint Board. One visitor, having expressed kindly interest in our displays, added 'but why not work on gallstones? There's a subject for you!' I would not dissent. But what in fact had been going on? Mostly little bits of smooth muscle, responding to the usual pharmacologist's drugs, in his usual organ baths. Some of it was groping towards what we now call the opiate receptor. Some was a first step, which, with many other steps elsewhere, would cause receptors to be taken more seriously, so that they would come to be counted, labelled, purified, used as antigens; now few major clinical centres lack receptor-binding studies of some sort envisaged or in play. Another step was J. R. Vane's development of a very sensitive biological assay, later to be one of a variety of such assays inserted into the circulating blood, allowing him and his colleagues to track down so many pharmacological transients inserted in the blood, and to open up so much that was new about the prostaglandins. The difficulty of assessing such work, 10 to 20 years remote from some of the applications to which it contributed, is that, unlike the latest drug new-hatched from industry, or the latest instrument, it can claim few proprietorial rights; it is always one of many such contributions, and it needs an experienced eye to see what happened. Yet it is this type of work, scattered round many modest laboratories, whose ultimate fulfilment is, at the time it is done, quite unknown, which seems to my eye absolutely vital. It is the very moment when a great flowering is in progress that these seedlings of unforeseen future flowerings, decades ahead, are most vulnerable.

The third great predator is lack of imagination. I do
not refer to the way that over-writing, over-meeting, over-organisation could be thought to threaten individual originality and individual differentiation, and to develop a sort of death by homogenisation (everyone chasing the same ideas), a socio-psychological entropy death long before that predicted by Jeans. The much simpler fact is that we get used to things. I think Osler got so used to the morbid anatomical appearances he knew so well that he could hardly envisage their abolition. Yet, if one looks at some of the records of the past, say Addison’s disease, confluent smallpox, lupus vulgaris, or Hodgkin’s disease, the fact is, for Great Britain, and potentially everywhere, those appearances have been abolished. So, too, we can become inured to accepting chronic neurological disease, allergy, psychiatric disorders, self-poisoning, arthritis, cerebral damage, congenital defect, blindness, deafness, as things we can do a little about, but do not really envisage abolishing. One of the great potential gifts of therapeutic research is the imaginative drive to believe that changes, as great as have been seen, are still to come.

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