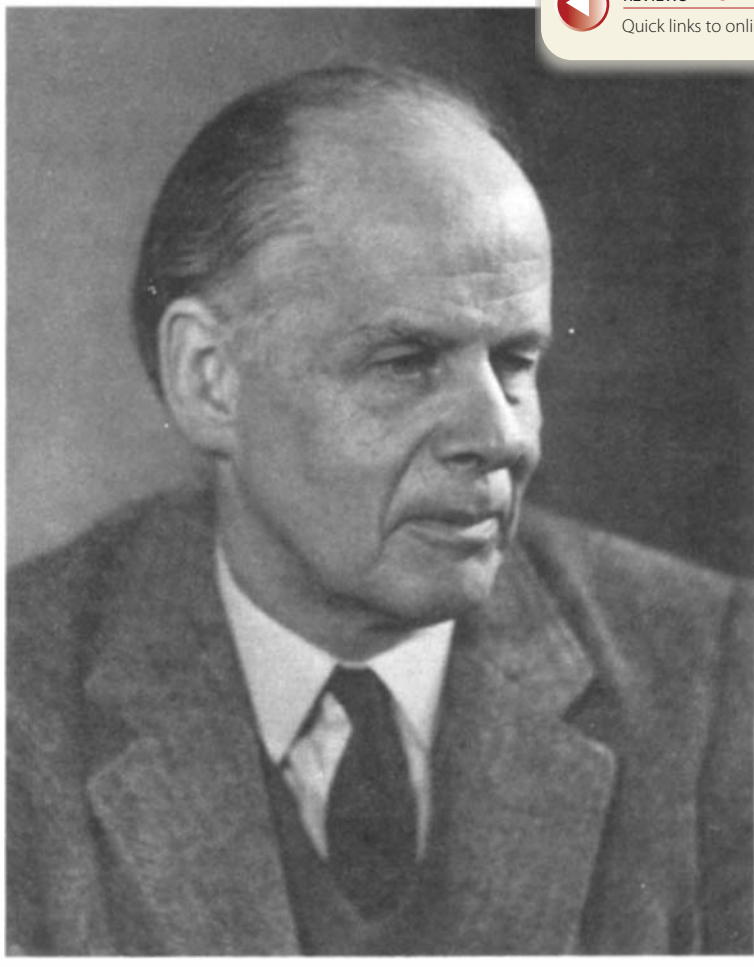

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Ann. Rev. Pharmacol. and Toxicol. 1986. 26:1–22

ON BECOMING AND BEING A PHARMACOLOGIST

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FINDING THE SUBJECT

Like others of my generation, I found my vocation of pharmacology by chance, having originally intended to go into academic medicine. In the 1930's, medical students received teaching in the actions of drugs, but the days of undergraduate degrees or later course work in pharmacology lay far in the future. So I was essentially self-taught, with all the freedom, but also the ignorances of the autodidact. Indeed for much of my life I have been among those with a similar background, not a few of whom would say that they were not "really" pharmacologists, but physiologists, biochemists, pathologists, chemists, or some other species. It was therefore not surprising that there was a good deal of discussion, on faculty boards and elsewhere, about the nature of the subject. I came to recognize that it is the sign of a newly developing discipline to be mildly obsessed with what it "really" is, and to be concerned with establishing an identity. Toxicology is going through something of the same process today. The resistance of established subjects to the emergence of new ones is an old story—going back at least to the opposition to the formation of the Geological Society by Sir Joseph Banks (president of the Royal Society) in the last century. Physicists and chemists seemed lucky; they did not need to ask such questions, which had been settled long before, but could get on with the work.

Nor was some discussion about the nature of the discipline unjustified. Pharmacology has a taproot stretching back into the remote past of man's attempts at healing; but it also has more modern roots. So pharmacology did not lack for those ready to explain that it was "only" a branch or application of physiology, medicine, chemistry, or biochemistry. Like any other discipline, pharmacology needs constantly to renew its vision. For me, the character of the

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subject seemed obvious and most of the formal definitions failed to express what it was that caught my own imagination. Before giving my own definition, let me mention how I was caught.

I suppose it was chance that, at the end of my medical residency, after qualifying in medicine during the London "blitz", I had a fifth attack of pneumonia (following a checkered pulmonary childhood). Medical investigation thereafter pronounced me unfit for military service, and also cast doubt on my capacity to do the residencies required for a career in medicine. The immediate outcome, after I failed to get a job at the Brompton Hospital, was that I took a post as a pathologist in a tuberculosis sanatorium. There was a brief training by a London pathologist, Dr. S. R. Gloyne. (It is somewhat ironic that his main life's work was trying to persuade an unbelieving world that asbestos damaged the lungs.) As was customary at that time, I was then on my own, doing sedimentation rates, blood counts, and culturing sputum or pleural fluid for tubercle bacilli. Occasionally I prepared lung biopsy specimens to assess the presence of cancer cells, and Gloyne would check my conclusions. The work was interesting, but my superintendent was an abrasive character, and I did not get on with him. By chance, a nephew of the then Secretary of the Medical Research Council was also on the staff. It was through him that, for the third time, I was offered a job at the National Institute for Medical Research at Hampstead. I had put previous offers aside, wishing to do clinical work of some kind. But now the offer was a relief and I accepted. On my last night at the sanatorium, I told my superintendent what I thought of him, which I had been too naïve to do before. He beamed all over, for he was one of those that like to challenge others; he then said he hoped to start a tuberculosis research unit at the hospital, and asked me to stay on and start it. I refused, but that was perhaps my first adult lesson in distinguishing between appearance and reality.

So off I went to work under G. L. Brown in Sir Henry Dale's old laboratory, joining in their wartime work on diving and submarine problems. I will say a word about the laboratory later. For the moment it will suffice to say that when peace came, the laboratory turned back to its old activities, and I began to turn into a respiratory physiologist. But then F. C. MacIntosh, the second in command, was asked by another member of the Institute, R. K. Callow, to look at the toxicity of an antibiotic that his group had isolated, named licheniformin. MacIntosh asked me to join him, and we started by testing the hydrochloride for its effect on the blood pressure of a cat under chloralose. It produced a quite characteristic response: no action for around 30 seconds and then an abrupt but fairly transient fall in blood pressure, often marked by a tachycardia during the recovery phase. It was a fascinating picture; for the initial latent period meant that the drug had no direct vasodilator action or cardiodepressant action, yet when the fall came, it was as abrupt as that produced by an equidepressant dose of histamine or acetylcholine. What was going on? In itself the simple tracing

pointed to the answer: that the drug released a vasodilator from the periphery, which, on recirculation, produced the fall in pressure. It could hardly be other than histamine if it was to persist long enough in the blood. A sample of blood taken from the animal at the nadir of the blood pressure produced an abrupt fall, of 5 to 10 second latency, due to a substance with histamine's properties. J. A. B. Gray and I later verified the circulation times involved.

So licheniformin turned out to be a histamine liberator (1), and I had had the good fortune to see a new, clean, surprisingly specific pharmacological response, which was in itself rather attractive as a tracing. When we went on to find that the same pattern was displayed by any dibasic compound in which the basic groups (amine, amidine, isothiourea, guanidine) were separated by around 6 or more carbon atoms, I was fascinated. A clean action caused by a specific chemical structure opened a new world. I have sketched elsewhere (2) how the follow-up led to the work with Nora Zaimis on the methonium compounds (3). Phenyl biguanide and Compound 48/80 were other dividends. The point, however, is that the fish was caught. That experience and what it led to is the basis of my own definition of pharmacology:

> If physiology is concerned with the function, anatomy with the structure, and biochemistry with the chemistry of the living body, then pharmacology is concerned with the changes in function, structure, and chemical properties of the body brought about by chemical substances. In the same way, pathology is concerned with the changes brought about by disease. For pharmacology there results a particularly close relationship with chemistry; and the work may lead quite naturally, with no especial stress on practicality, to therapeutic application, or (in the case of adverse actions) to toxicology.

Such a pattern seems to me both to do justice to what catches the imagination of those working in the different fields, as well as showing how they all belong to one family.

Do such definitions matter? Most of the time not. But in the recruitment of new blood, it is useful to have some shorthand description; and when it comes to higher policy, the nonscientific administrator is liable to define pharmacology, just from its etymology, as "the science of drugs", with a resulting difficulty in distinguishing it from pharmacy.

Competition for funds, or simple enthusiasm for a subject, often leads to exaggerated claims for a particular discipline, and to the view that other subjects are inferior or merely applications of it. (Sentences containing "merely" or "only" should always be viewed with deep skepticism.) I like to reduce such claims to an absurdity. Let us start with pharmacology;

> which may be said to be merely applied physiology;
> which is, of course, merely an embodiment of biochemistry;
> which is merely chemistry in one development;
> which is merely the working out of certain physical principles;
> which is merely the body of particular solutions of certain mathematical equations.

> But mathematics is only a branch of logic, as Bertrand Russell and his peers established, so that philosophy is the fundamental basis of it all.
>
> Yet we know today that philosophical ideas are culturally determined, not absolute, so that sociology is the central discipline.
>
> But sociological thinking must be merely a function of psychological process.
>
> Such processes are, of course, no more than exercises in the pharmacology of the central nervous system.
>
> The whirligig is complete.

Pharmacology, then, can take its own place. There is no one science central to all the others, as various scientific chauvinists would have us believe.

It is equally untrue to real life to say that "all science is one". That suggests a sort of homogenized intellectual mayonnaise, with no differentiation. One can, of course, trace relationships, as indeed I have just done. But each scientist seems to find something particular that catches his imagination. The disciplines that become separate, for the time being, are those areas that seem to fire enough people, are attractive enough to the young, and are worth meeting for, thus creating a kind of mental center of gravity. One need not be exclusive, but can move between one center of gravity and another.

If one asks, when did pharmacology begin, perhaps one can place the start in the remote past of *materia medica,* or with Magendie's first analysis of the action of a drug, or with the founding of chairs and societies, or with the therapeutic explosion from the 1930s onwards (4). But historically, the Stockholm Congress in 1961 now seems to me one of the watersheds. Börje Uvnäs had asked me to join its organizing committee; and there followed a fascinating discussion of the program to be developed in pharmacology's first independent international meeting. It was a critical moment. That meeting might have fallen apart into its biochemical, physiological, chemical, pathological, toxicological groupings. But it did not; the great and marvelous fact was that despite misgivings it fell triumphantly together. The establishment of pharmacology as an independent discipline, a center of gravity in its own right, was certain from then on.

As for my research on diving, I can see now that it too had a pharmacological component. For instance, there had been operational reports of what was called "shallow water black-out", and one of our concerns was the risk to a diver (and also to those in a sunken submarine) of becoming unconscious through CO_2 accumulation. It had previously been thought that respiratory stimulation would always provide sufficient warning, but we had found that if sufficient oxygen was present to remove any hypoxic drive, as was normally the case in diving, then CO_2 could produce unconsciousness readily (even pleasantly) without gross respiratory stimulation. It fell to me to run the O_2/CO_2 mixture breathing experiments to define the range of individual sensitivity.

All the members of the laboratory "blacked out" in their turn, as did any

unwary visitors, such as B. H. C. Matthews and D. G. Evans. Judging by subsequent careers, a few minutes of 10–20% CO_2 has no long-term toxicity. But the experiments led to reading about anesthesia. Then G. L. Brown asked me to join him in advising some civil engineers on compressed air work, which resulted in collaboration with D. N. Walder and others on "bends". So an interest in high pressure biology was implanted that survived even when wartime work was all wound up. That interest produced, with E. B. Smith, a colleague in physical chemistry, the Oxford High Pressure Group; and the research still, in the problems presented by the "rapture of the deeps" and the High Pressure Neurological Syndrome, has its pharmacological flavor.

For those whom it suits, pharmacology is a lovely subject, carrying one quite naturally from the molecular level to the whole man, using any and every skill one possesses, intellectually demanding yet with practical usefulness round the corner, not yet too sophisticated technically, and still young and fresh enough for the simpleminded to be able to contribute.

"F4"

Sir Henry Dale's laboratory, the Division of Physiology and Pharmacology, in the National Institute for Medical Research in Hampstead, was one of the classic laboratories. It deserves study in its own right, and I hope that those who worked there have left some account. A latecomer like myself, though deeply influenced by it, can only give a hint of what it must have been like in its prime.

The fourth laboratory on the first floor, it was, in 1944, a large communal laboratory. If one's own experiment was not going too well, or there was a waiting period, one could look at someone else's. The storage cupboards full of equipment reached up to a high ceiling. That ceiling was stained from the overflows in the organic chemistry laboratory above. When we rolled cylinders of gas on the floor, to make new mixtures to breathe in the diving experiments, protests would come from readers in the rather beautiful Georgian-style library below. A small side room contained a bicycle ergometer used for studies at controlled oxygen consumption. The laboratory was entered from a corridor that ran the length of the building, and there was a small office, a small workshop with a lathe and hand-tools, and a lavatory immediately across the corridor. One of the pleasures was that if one went out into the corridor one was only too likely to bump into someone from one of the other laboratories.

The main laboratory was simply laid out: There was a long window bench looking out over the tennis court and other grounds, the Institute's main workshop, and the shed housing J. S. Haldane's old compression chamber, recently transferred from the Lister Institute; desks, arranged according to the inhabitants and needs of the moment; operating tables and kymographs; an old watercentrifuge with a balance for its cups and a stern notice from the head

technician above it: "Near enough is not good enough"; paper-smoking and varnishing cabinets in one corner, adapted during wartime to accommodate a Haldane gas-analysis apparatus; a refrigerator, oven, waterpumps, and so on.

At lunchtime we could join other members of the Institute in the lunch room at the top of the building and then go through to the coffee room, which had a balcony looking south over the rest of London. Towards the end of the War, when the time of the "doodlebugs" came, one could see the defensive barrage balloons on the Downs. Across the road outside the Institute was the pub, the "Hollybush", where one could take a visitor after work in the evening or have some celebration.

Between 1944 and 1949, when the Institute moved to Mill Hill, H. B. Barlow, J. A. B. Gray, B. D. Burns, and W. L. M. Perry were other members of staff; M. Goffart, J. L. Malcolm, A. Sand, M. Vianna Dias, and Nora Zaimis were our honored visiting workers.

The head technician, L. W. Collison, had been Dale's personal technician, and was of kindred quality. Not greatly educated, of rather gloomy appearance, formal, courteous, tough, a stern disciplinarian, yet as determined to stand up for his staff's rights as for his own, he was intrinsically very kind, and a man of the highest standards. These he displayed in his preparation for experiments, in his construction of exquisitely delicate Brodie bellows for sensitive plethysmography, and above all in his preparation and mounting of smoked drum tracings for publication. Many of the classical tracings in the *Journal of Physiology,* establishing the theory of chemical transmission, attest to his artistry.

How does one pin down the intangibles that create a successful laboratory? You were expected to stand on your own feet. Yet there was every kind of support by advice, criticism, personal help, and (most notably) general pleasure at any progress you made. No feasible experiment, if you wanted to try it out, was barred. The range of equipment available and the little workshop across the corridor made it easy to develop a new technique. But perhaps the secret lay in the two at the top, both of whom had shared in the *anni mirabiles* of chemical transmission before the War. G. L. Brown ran the laboratory on a very light rein and gave the laboratory high spirits and a wonderfully deft experimental skill—he was a joy to watch. F. C. MacIntosh exhibited a depth of thought and an unquenchable considerateness in everything he said and did. It is impossible to set down what one owes them.

INTO A WIDER WORLD

In 1949, with the move of the National Institute to Mill Hill, G. L. Brown went to the chair of Physiology at University College, F. C. MacIntosh to that at McGill, and W. Feldberg took over "F4", establishing its ethos in a new

environment. We worked together on histamine release from skin; devising a perfused skin preparation and learning how to write papers with him were equal delights. (To describe our consumption of cigarillos would, today, doubtless count as pornography.) There was also collaboration with Burns (on endplate depolarization), with Perry (on ganglia), and with new recruits such as W. W. Douglas (on anticholinesterase effects) and M. Schachter (on the effect of antihistamines on the release of histamine), as well as writing papers with Nora Zaimis.

The Director, Sir Charles Harington, was always slightly irritated at comparison with the Hampstead days; yet W. A. H. Rushton's remark, that "moving to a larger laboratory is like an adiabatic expansion: the particles become more distant from each other, and the temperature falls", seemed to have some truth. One bumped into members of other sections less often. Yet it was, in fact, during a corridor conversation that Albert Neuberger remarked to me that he felt his work was not going very well, and perhaps he ought to move. A year later, a chair at St. Mary's and a burst of new work thereafter showed his wisdom.

I am not quite sure what generates this restlessness, which I was feeling, too. The wish to be one's own master does not seem sufficient cause, when one has so much freedom and such facilities. Perhaps, for an experimentalist, it is more the wish to have a shot at doing a new experiment, to head a department oneself. For me, it led in 1952 to a Readership in Applied Pharmacology at University College Hospital, joined by J. W. Thompson, under two professors, M. L. Rosenheim in Medicine and F. R. Winton in Pharmacology. The laboratory was embedded in the Medical Unit, with an additional small room across the road in University College, and £200 a year running expenses. Our formal responsibility was to help Heinz Schild with his practical class in the College, and to give a course of 20 lectures bridging the basic pharmacology taught by Schild and the therapeutics lectures by physicians (that also fell to me to organize). It was quite a challenge to produce a complete lecture course after life at an institute. Work on histamine release went on, and John and I had an interesting time with A. Goldberg testing porphobilinogen, which had been recently isolated from patients with porphyria by R. G. Westall, to see if it was a possible causal agent of their symptoms. Unfortunately it proved rather inactive.

After two years, however, a serpent appeared in the Eden, namely C. A. Keele, with an invitation from the Royal College of Surgeons to start a new department of pharmacology there, for postgraduate teaching. By then I had had many contacts with anesthetists and physicians over the use of the methonium compounds and it seemed to me self-evident that no undergraduate course could possibly equip a medical student with all the basic knowledge he needed in his career—there was too great an annual flow of new drugs and new

procedures involving totally new principles. So the idea of postgraduate education, of teaching those already experienced in medical practice who wanted to be updated, made sense. So did the idea of fuller laboratory resources.

In this academic experiment, John Thompson (now in Newcastle), John Vane, and John Gardiner (now in Hong Kong) joined me. I couldn't have asked for anything better than to start a new laboratory with such colleagues. It is remarkable to me now, when academic tenure is so much discussed, that it seemed to matter little to us that I was losing tenure and they were not receiving it. There was only enough money for the new laboratory for 5 years, and its continuance depended on our success. We were lucky with our research fellows and associated staff, all from the clinical world: J. G. Murray, E. Marley, G. C. Clark, and J. P. Payne, later to occupy chairs of surgery, pharmacology, surgery, and anesthesiology, respectively. Of our visitors, B. B. Gaitonde went on to head the Haffkine Institute, and Emile Savini to chairs in France. It was a very happy time, and it was the best interaction of "basic" and "clinical" science I have ever had. That the department did indeed continue, under Gustav Born, John Vane, and Graham Lewis, has always pleased me.

The Royal College of Surgeons broadened my life, but the effect was nothing compared to that of the move to Oxford in 1959. As an Oxford graduate, one was "imprinted" by the University and one's old college; but the experience of an undergraduate, "the toad beneath the harrow", and of one of the dons, the "harrow" itself, is very different. It is too much to describe here, and indeed, it is still in process.

But there are two things from my time at Oxford that I like to mention. The first arises when aspersions are cast on the academic standing of pharmacology. Then I like to recall that in 1962, out of an established staff of six, four were Fellows of the Royal Society: E. Bulbring, H. Blaschko, H. R. Ing, and myself. That is in part a tribute to my predecessor, J. H. Burn, but it seems to me also to show that quality is not impossible even to a small science. Other departments can make equivalent claims.

Second, I have concluded from 25 years at an undergraduate university, as well as from seeing many other forms of research life, that no research institution keeps its freshness and vigor, unless it is continually rinsed through by exposure to new youthful minds. The undergraduate can be infuriating, lazy, stupid, and rude (and also charming, hardworking, intelligent, and courteous). No doubt he feels the same about his seniors. But there is something uniquely invigorating in being obliged to interest minds quite new to a subject, and to respond to the naïve, sometimes foolish, but essentially unspoiled vision of it that they have. New centers of research, free from the "burden" of teaching and the associated tasks, can flourish for a time. But follow their progress over the years, and you will see the complacent inward look developing—unless some wise person has contrived a youthful revivifying stream.

RATE THEORY REVISITED

I am sometimes asked what I think about rate theory today. The question always drives me back to the mental puzzles that evoked it.

The idea of rate theory germinated around 1955. The immediate stimulus was an invitation to give a paper on the mechanism of neuromuscular block at the World Congress of Anesthesiologists in Scheveningen that year. The two types of agents, depolarizing and nondepolarizing, that Eleanor Zaimis and I had distinguished operationally in some detail, were familiar. But examples were accumulating of block of an intermediate type, such as what she called "dual block". Bovet had contrasted "pachycurares" and "leptocurares" corresponding (for example), to tubocurarine and decamethonium, thus emphasizing the role of molecular shape. But the intermediate type of response, with typically stimulant phenomena followed by apparently simple curare-like block, was found even with a "leptocurare" like tridecamethonium. I included in my paper (5) a crude estimate of polarity of the various agents (the ratio of C atoms to N atoms), and suggested that when the ratio rose above 8 to 10, a transition occurred from depolarizing to intermediate type. It therefore seemed to be progressive hydrophobicity that caused the development of a curare-like component of action. The survey suggested that "drugs with some measure of hydrocarbon loading may (through their lipoid affinity) develop an attachment to the membrane of a kind different from, additional to, and interfering with, the attachment which leads to endplate activation. For instance, it might be essential, for normal activation, that a chemical bond be rapidly made and broken, or that the molecule has to move across or through the membrane; fixation of the molecule by its hydrocarbon content to adjacent lipoid regions of the membrane could well interfere with such a process".

But the problem of dual block was not the only stimulus. The work on the methonium compounds had raised in an especially acute form the question of how it was possible that structures so closely alike as hexamethonium and decamethonium could not merely act selectively on different effector organs, but act in totally different ways. Work with W. L. M. Perry had revealed the action of nicotine on the ganglion also to be of intermediate type, with depolarizing block passing over to a nondepolarized hexamethonium-like state; and on the guinea-pig ileum the self-block and bell-shaped dose-response curve were not well understood. Study of the anaphylactic spasm of sensitized ileum, and the extent to which it could be imitated with histamine, also raised some puzzles. Finally, there was a long-standing wish to describe the time course of recovery from neuromuscular blocking agents, ever since our finding, during potency comparisons of decamethonium with tubocurarine, that after apparently complete recovery of a muscle twitch from tubocurarine there might still be enough tubocurarine left to antagonize the action of decamethonium.

I was, however, at that time almost totally ignorant of receptor theory (what there was of it), and had just started a notebook devoted to the subject. It is hard today to understand the paucity of knowledge about, and the almost antagonistic attitude to, the receptor concept at that time. For a start, my greatest help was Haldane's 1930 book on enzymes, to which I turned after initial study of adsorption isotherms in a textbook of physical chemistry. In due course I found Gaddum's 1926 paper, then Clark's monograph of 1937, and Gaddum's formulation of competitive antagonism in the same year. Then there was Schild's pA notation in 1947 and 1949. But there were also a number of papers incompatible with Gaddum's formulation, and in the background were, for instance, the critical remarks by Dale in 1945 of the whole receptor concept, and a conspicuous lack of any direct evidence for it. In 1954 there began a long series of papers by Ariens and his colleagues, developing for drug action a framework comparable to that available for enzyme kinetics. By hindsight, these could have helped me; but at the time the multiplicity of possible models presented, with a growing number of disposable parameters, left me rather confused. I found myself more at home with R. P. Stephenson's work published in 1956. But although his introduction of the concept of efficacy seemed a real advance, it did nothing to answer my question of why some drugs are stimulant, some antagonistic, and some intermediate. To say that efficacy was high, low, or medium just restated the problem.

I think it is unlikely that I would have gone much further had not a bronchial episode led to a period in bed, around 1956. For something to do, I started working through for myself the equations that a bimolecular type of reaction may lead to, particularly seeking formulations that would be experimentally testable. I looked for patterns that could explain the bell-shaped dose response curve of nicotine on the gut, that would give some physical interpretation of efficacy, that would explain the transition from stimulation to relaxation with intermediate-type drugs, and that would help to analyze the time course of blocking agents in the body. Haldane and Briggs' analysis of the results of a two-point attachment, with a bell-shaped substrate concentration-velocity curve interested me very much, and I was carried far out of my depth in trying to extend it and its kinetics. I made rather little progress. When the thought finally occurred that receptor excitation might be a function of rate of association of drug with receptor, it seemed almost magical how many of the questions it solved. If activation of the receptor required that a high rate of drug turnover continually releases receptors for fresh associations, then the characteristic sequence (stimulation then block) of intermediate drug action followed naturally, drug-receptor dissociation rate could provide the independently measurable index of efficacy, and the slowing of dissociation by hydrophobic bonding explained the shift from stimulation to block with increased hydrophobic loading in homologous series.

It was quite a busy time in other ways. There was the move to the Royal College of Surgeons in 1954. From 1951 to 1957 I was secretary of the Physiological Society. In 1959 I moved to Oxford. Most of my experiments were performed in the evening and it shows. There is not nearly enough replication in the paper that I finally wrote (6). It would have been wiser, too, to have separated more distinctly the various themes in that paper. I felt the phenomena of nonspecific desensitization of smooth muscle were important, that they showed that nonreceptor effects could be great and needed to be controlled, and that they seemed to provide an immediate explanation of the existence of spare receptors (for they meant that receptor occupancy would not always be the rate-limiting step). This last point, however, was really a separate issue.

I would treat the ion exchange model differently today. There is no evidence that it plays any role, although I still wonder about the fate of counter ions to charged groupings in the receptor in the presence of an interacting drug. The model was only suggested, because it seemed to me necessary to give some illustrative example of a possible quantal mechanism. MacIntosh and I had considered an ion-exchange mechanism for the action of histamine liberators, with the bases exchanging with histamine in the tissues. So, in my reading round the subject of neuromuscular block, I had noticed Ing and Wright's suggestion of an ion exchange by alkylammonium salts at the neuromuscular junction. It was a simple concept that had stuck in the memory. Finally I was impressed with the evidence about loss of potassium as a result of agonist action. But again, it was a side issue.

Rate theory had its first exposure to the British Pharmacological Society in July 1959. Then, in 1961, I was asked to present the paper before publication at a meeting of the Royal Society, which I did, loaded up with analgesics. The President, H. W. Florey, asked Gaddum, who was present, if he thought the theory was sound, and Gaddum replied that he thought there might be something to it. Bernard Katz asked what quantal mechanism I envisaged. I could only repeat my working analogy, that the drug-receptor interaction was more akin to the playing of a piano (where a finger that is not rapidly withdrawn interferes with the flow of sound), than it is to the playing of an organ. That weekend I went into Hammersmith Hospital for a bilateral antro-ethmoidostomy. One of my pleasantest memories was at a meeting of the British Pharmacological Society around that time, at which John Vane, describing an experimental set-up, referred to "what I understand we must now call an isolated piano bath".

What does one think of the theory now? I think it helped to promote interest in receptor studies, particularly on the kinetic side. I still find its economy conceptually attractive, requiring as it does only two rate constants and one other constant to couple the receptor to the effector. So far, I see no other

independently testable interpretation of efficacy. As a possible model it does not seem to mislead the student, since most of its consequences for the general pattern of drug action are quite sound: agonists do wash out quickly; for equiactive doses, antagonists do usually take longer to act and to pass off, the more potent they are; decline of antagonism can be measured, and changes in receptor occupancy do follow an exponential course. With partial agonists, agonism is prompt and then antagonism follows; hydrophobic loading does generally favor antagonist rather than agonist action.

I was very disappointed that the measurement of the rate constants of drug receptor interaction has proved so difficult, particularly with smooth muscle, where the range of values seems wider (and thus potentially more informative) than with striated muscle. It was ironical that it was our own work at Oxford (7) showing how the relatively large uptake of drug by the receptor created a large reserve of drug, that led to the possibility that the kinetics were diffusion, not receptor, controlled, as Douglas Waud had come to suspect and Thron and Waud then showed (8). No way was found to distinguish the two possibilities. I was back in the old position, unable to find a definitive, objective, independent sign of efficacy.

It is pleasing that agonist action has now turned out to be quantal, and it seems likely to be linked to receptor turnover. But it seems uncertain how the quantum originates, whether from the allosteric behavior of the receptor or from some aspect involving the drug molecule too. It was also interesting that an identical theory was formulated within gustatory physiology, quite independently, but for similar reasons.

My guess, however, is that the deeper understanding of the kinetics of drug action is not going to come through the formulation of drug-receptor equations, but from qualitatively new observations. Patch-clamping and conductance-channel biophysics, molecular engineering, and ultramicroscopy offer fascinating openings. I have suspected that our formulations will prove far too simple, ever since seeing some of D. C. Phillips' X ray crystallographic pictures of the interaction of a number of different substrates with lysozyme. With each substrate, the interacting regions were subtly different. Presumably the same is true with drugs interacting with receptors, and the reactions that we blithely represent by a single equation, $D+R \rightleftharpoons DR$, are in fact all different.

ON DOING WHAT YOU ARE ASKED TO DO, AND THE STIMULATED ILEUM

I have already mentioned two lines of research that followed on an "outside" stimulus—histamine liberation and rate theory. This is an important phenomenon, weakening the concept of the autonomous scientist in his ivory tower; even in research he seems to need stirring up from time to time. A third example

was an invitation to talk on the pharmacology of the small intestine at a Gordon Conference, presumably because of my ganglionic work. I knew little about the gut, and found considerable doubt in the literature even as to the transmitters. So I began to search for some way of making a "neuroeffector" preparation out of a strip of intestine, on which one could do analyses comparable to those on striated muscle or ganglionic preparations. N. Ambache had found that a strip of gut would twitch if an electric stimulus was applied to its surface. But one then finds that the point of excitation moves and is undefined. It was then that I recalled some old experiments by Rushton, dealing with Lapicque's chronaxie theory of curare action, and Du Bois Reymond's cosine law: that excitation of a nerve in an electric field is in proportion to the cosine of the angle between nerve and field. Suppose one placed an electrode in the lumen of the gut, another outside, and created a field between them. The field would now be defined, independent of gut movement. But would the nerve networks of Auerbach's plexus be at an angle to be excited? The first experiment, in my office-cum-laboratory at the College of Surgeons, is still vivid. I set up the Trendelenburg preparation used to study peristalsis; my only piece of platinum, soldered to a lead, was threaded into the lumen. An alligator clip, dipping into the outer bath fluid, provided the other electrode. It worked like a bomb, with shocks as short as 50 μsec. I had, in a few moments, both a new neuroeffector test-bed (9), and something to say in New Hampshire. G. L. Brown, when he heard about it, was very amused, and called it the "electric clyster" in a mock eighteenth century poem. He also sponsored it for a demonstration at a Royal Society soirée, at which Fellows were able to do an Otto Loewi-type experiment for themselves: they took fluid from one bath holding an eserinised strip of intestine, with or without stimulation, and tested it for acetylcholine content on a second comparable strip arranged for assay.

The guinea-pig ileum longitudinal muscle is a great gift to the pharmacologist. It has low spontaneous activity (unlike rabbit or rat); nicely graded responses (not too many tight junctions); is highly sensitive to a very wide range of stimulants; is tough, if properly handled, and capable of hours of reproducible behavior. A further bonus appeared later when I did electron microscopy on it, and found that Auerbach's plexus lay on the surface of the longitudinal muscle, not penetrating into it. As a result, after Humphrey Rang had shown how to separate strips of longitudinal muscle, Aboo Zar was able to produce acutely denervated strips simply by pulling them off the plexus (10). I know nothing quite like these preparations in physiological pharmacology. Normally, to denervate one cuts a nerve and then waits for it to degenerate; but during that time profound changes take place in the postsynaptic structure, so that one does not have a perfect control. The longitudinal muscle of guinea-pig ileum, with its diffusive type of transmission, is the only tissue I know of that allows you rigorously to compare innervated and totally denervated muscle. This was

particularly important at the time for making absolutely certain that the acetylcholine released came from nervous tissue, not muscle. I had found that morphine inhibited the ileum twitch without affecting the response to acetylcholine and reduced ACh output (11), I was now confident in the conclusion that morphine was acting on nervous tissue and that the ileum could be used as a "paradigm of the brain."

The preparation has proved admirable for teaching. The coaxial method of stimulation was only necessary when stimulator power was limited, and simple field stimulation proved to work admirably. Particularly enjoyable was the collaboration with Sylvester Vizi on the effect of catecholamines on transmitter output, opening up a profitable presynaptic vein (12). So has been its use in identifying and assaying opioid peptides and drugs. Perhaps every scientist should be asked to talk on something about which he is ignorant, every five to ten years or so.

COMMITTEES

In my best, or worst, year, I counted service on 72 committees that met at least once, and sometimes ten to twenty times, in that year. I am sure there are others with a similar experience. It seems too many, yet none of them was trivial. The most severe critics were those who wanted me to serve on a seventy-third. Is there anything to say about it, except to warn?

It does require a decision at some stage in one's life. When the invitation first comes, it is not unflattering to find that somebody actually wants your services. Most people would agree that democracy, with continually changing committees, is in the end better than dictatorship or oligarchy. There is, too, the opportunity both to be more "in the know" and to have some influence. Most people find a small dose of one or the other attractive enough to exchange for a little research time or some leisure. In the event, you do indeed lose time, and it can be trying to spend hours awarding money to others to do experiments you would like to be doing yourself. Some say discouragingly that such work is "all right for those that like it". It is a great simplification when you grasp that the only valid reason for doing anything is that it is the right thing for you to do. There is in the end a genuine satisfaction in seeing work progressing that you helped to forward. Even more important, and a reflection of the fact that shared endeavor is the most potent source of friendship, are the friends you make. So, if advice were wanted whether or not to undertake such work, the heart of it must be the importance of diagnosing one's own capacities and values. It proves to be a balance between one's own work on one side, and, on the other, new friendships while forwarding the work of others. Not a very obvious choice. I recall a famous remark by F. M. R. Walshe, the great neurologist at University College Hospital, a Catholic and vigorous controversialist for whom I served as house officer. After seeing a pair of outpatient twins he said, "I wish

one could baptize one twin and use the other as a control". (If we could live a second life, would we go back to do the controls to the choices we have made?)

Nevertheless, committee work can certainly go too far. I suspect that pharmacology may be especially vulnerable. The pool of trained pharmacologists is in any case not very large. The academic part has to teach doctors, physiologists, pharmacologists, biochemists, chemists, and pharmacists. It has to attract students, arm them with an undergraduate training, introduce them to research, and then supply them to industry as new recruits to an extent that the other preclinical sciences are not called upon to do, proportionate to their total numbers. It must also supply the research leaders for industry. In the United Kingdom, I reckon that industry has taken away from academic life men who would have filled about a third of the professoriate. (By and large industry does not repay to academia its training and recruitment debt, despite the great scientific contributions of industrial pharmacologists.) That brain drain cannot strengthen the remaining pool to whom it chiefly falls to provide the general servicing (and defense) of pharmacology in its private and public functions. Finally, the sheer usefulness of pharmacology frequently brings its practitioners into practical affairs and issues that call for expert advice.

It would be better if the work was shared more widely. Committees might more often invite younger scientists to serve, instead of relying largely on older people. This would widen the decision-making base, and keep the decision process nearer to the front line of new knowledge, the true source of freshness and invigoration. Getting the right balance between age and youth is quite an art. It is wrong to burden the young while they are still establishing themselves, and while they are in a particularly fruitful phase. They also may lack patience. The old often have a mass of useful case history to call on, and have seen many "experiments" tried. Yet there is a tendency for old men to fight old battles; and while sometimes those battles are over issues that are still alive, too often the arena has moved elsewhere. I can see no rules, except perhaps to prefer for service those who are a shade reluctant to serve.

Secondly, it would be interesting to try building into the standing orders of any committee a terminating rule, that it must be disbanded after three years unless a really strong positive case for its continuance is made.

Thirdly, when a statutory committee simply must meet, it should be expeditious. My best example is my old "boss", G. L. Brown, whom I saw get through a statutory faculty board meeting at University College in 1.5 minutes flat, having accomplished all the required business.

CHOOSING AND JUDGING

Among the most important of committees are those concerned with making choices over appointments and awarding grants. I must have been involved in making hundreds, if not thousands, of such choices. Some years ago I was

suddenly struck with repugnance at the whole procedure; and I wished never to make a judgment on another scientist again, nor have it in my power to influence his career in any way. Unfortunately one cannot responsibly just contract out. I suspect it was a reaction that was shared by others, for a general movement has occurred toward examining the efficiency of the decisions made by grant-giving bodies, and toward testing the validity of peer review.

For some time I have made little lists, as opportunity offers, of two things. One was of the names of those whom I had helped to choose for positions, together with their competitors' names. The other was of unforeseeable events (for example an unexpected death of someone in a key position, or a surprise career decision). Taking the approach of the naive empiricist, as opposed to that of the a priori thinker, I hoped that the first list would allow me to look back and see how wise a choice had been and that the second would enable me to test how far decisions seen in hindsight as incorrect could be understood as partly inevitable.

I cannot pretend to any great enlightenment. One thing that struck me was the mind's resistance to the idea that events indeed cannot be foreseen. My list of unpredictables has now lost all the impact each item had at the time it was entered; the choices now seem historically inevitable. Among the protective mechanisms of our minds there is something that rejects uncertainty and the cautious suspension of belief that an awareness of uncertainty requires. Since then, I have been struck by the rarity with which, for instance, journalists are willing to suspend judgment. In public utterance, the "all-or-none" law operates, with premature polarization and sharp antithesis clouding the possibility of any intermediate ground on public issues. Perhaps that is one reason why the scientist may find public affairs difficult.

A second thought was really a question, and it arises from the teaching and examining of students too. What is the proper time span for judging academic and professional performance? Should the competence of a medical student be judged by performance in an examination, in the first residency, after 10 years practice, or by the mortality rate among his patients throughout his life? Is a professor chosen for what he will do immediately, in five years, or over his whole career? Does one judge by the latest work of an individual, by the integral over his whole career thus far, or by some extrapolation into the future based on previous work?

Discussion of such questions does not prove very useful. One tends perhaps to favor that way of assessment that would put the best light on one's own work. But I do share the general suspicion of publication lists. The enormous growth of multi-author papers, and the breaking up of work into multiple papers, has made bibliographies extremely hard to interpret, and time rarely allows the reading of them. Yet if one sets them aside, what evidence is one to use? Referees are often flatly contradictory of each other and themselves need

refereeing. It is only a matter of luck if there is an authority on the topic in one's decision group.

I believe, however, that for career choices at least, there is information that could be better used. Among the signs of peer trust and confidence are: the appointment of an individual to editorial boards, or to some office in a society, or to be a representative of some sort, or to be an examiner, or to be an organizer of some meeting or event. Success with graduate students is another sign. In each of these situations, other scientists are entrusting some part of their own concerns to another individual. It is true that none of these tests directly measure, say, creativity. But it is also true that people do not entrust matters of these kinds to the ignorant, foolish, or unresourceful. If one looks back at office-bearers and editorial boards and the like, it seems to me that many of those whose research I have admired do indeed appear among the names.

I would not wholly abandon the Citation Index type of approach, provided one restricts oneself to well-refereed journals of substance, and corrects for self-citation. But I would also like a Scientific Service Index, which records those activities where a scientist has been chosen by his peers. My only gloomy thought is that, once established, the Law of Indeterminacy (that the act of observing a phenomenon itself changes the phenomenon) would operate, as it has begun to do with the Citation Index.

More important, now that we are so much in one another's hands, is to keep thinking about assessment. It is common enough for bodies to look backward at their successes. It will take more courage to extract the rejections and the alternative policies not adopted, and to examine the failures. A good clinical trial notes adverse reactions and deaths, as well as benefits and survivals. Why should one assess one's own past choices less rigorously?

THE SOCIAL RESPONSIBILITY OF SCIENTISTS

Do scientists have, by virtue of their skills and knowledge, any particular social duty outside their science? It is a sign of the times that the question would, today, almost always be interpreted politically, although it is equally valid at the level of individual action on behalf of other individuals. The answers are immensely varied, and the causes taken up equally so, whether nuclear war, preservation of endangered species, pollution in all its facets, holistic medicine, or civil liberties. There would likewise be no agreement about the range over which the scientist speaks with particular authority, and where with no more than any citizen's. He may like to claim an objectivity conferred on him by training and practice, but the nonscientist does not always find this convincing.

For my own part, I have been pushed out of the purely academic path over two issues. In each case what got under my skin was what seemed to me, to quote a phrase of my grandfather's, "suppressio veri and suggestio falsi". The

first was the antivivisection movement. Soon after I had qualified in 1942, I saw an advertisement by an antivivisection society on a hoarding near our flat in London. It claimed to give the number of children dying from diphtheria over a term of years, who had been vaccinated against the disease. None of the other relevant figures, about numbers at risk and the fate of the unvaccinated, were given. It stuck in my mind. Perhaps it prepared me for joint work while secretary of the Physiological Society, later as Chairman of the British Research Defense Society, and later still for writing "Man and Mouse" (13). Such tasks took time away from the laboratory; yet how could anyone who has seen what medicine can do as a result of animal experimentation, who then sees that work traduced, fail to defend it?

There may be a trace of genetic predisposition here—I am very proud of my grandfather. David Macdonald was a Presbyterian minister in Derby in 1901, when Stephen Coleridge, the leading antivivisectionist of his day, came to lecture on animal experimentation. My grandfather, who was interested in science and bought *Nature* every week to circulate round his parish, did not like the style of what he heard. He criticized it vigorously at the meeting, citing Ferrier, Keith, and Spencer Wells, and then wrote to the local paper referring to "suppressio veri" and "suggestio falsi" and saying that no lover of truth could support Mr. Coleridge's society. Coleridge then launched a suit for libel, demanding a public apology, damages and costs. Although David Macdonald was a poor man, he refused these. He had always been friendly with the local doctors, and in due course they came to his rescue, bringing in Lauder Brunton and Victor Horsley. When the case came up, David Macdonald needed to do no more than show that there had been no personal attack; after 30 minutes, the jury asked if they needed to hear any more, returned a not guilty verdict and said the case should never have been brought. It remains an exceptional case to my knowledge, of a member of the church putting himself at risk for the world of science. A gentle, affectionate man, he retired to the Scottish Highlands, and died after overtiring himself in the mountains. One of his sayings was: "You should not criticize people unless you have been in the same position and done better."

The other "outside" activity has to do with drug dependence. Work with morphine led me in 1966 to attend a meeting on adolescent drug dependence, where I heard about cannabis use for the first time. Two points were of interest. One was Dr. Rasor's remark that 95% of his New York heroin users had also used cannabis, but only 30–50% had used other drugs like amphetamine, alcohol, and barbiturates. The other point was the flat contradiction of one psychiatrist by another as to the reasons for cannabis use. So I went away to look up this curious material. What I found did not seem to correspond at all with some of the assertions being made (about harmlessness, lack of after-effects, nonaddictiveness, power to improve mental function, and the like). As

I then began to see the effects in students, my overwhelming feeling was that a vulnerable generation had been gulled. I felt some duty at least to publicize more of the original information, rather than allowing secondary and tertiary citations appear to be the sum of information available. This led to a good deal of lecturing (14) and some writing, and the discovery of Gabriel Nahas as an ally. E. W. Gill, R. G. Pertwee, and I started some work, which later was extended with mass spectrometry under David Harvey. No one can be happy about the incidence and effects of drug dependence today. But now, three satellite conferences (15) and many symposia and reviews later, there is at last some solid information, and the subject is no longer so briskly brushed under the carpet of sociological bromides.

As always, the work brought new friends. It also proved interesting in new ways, because of the political and media dimensions. It is irksome at first to find oneself classified by the antivivisectionist activists with slave traders and Nazi war criminals or by the "pot lobby" with Commissioner Anslinger. One learns the edge behind the advice "If you can't stand the heat, get out of the kitchen". But it is also fascinating to learn to what extent the dictum that "the medium is the message" is true. There is no doubt that a truly effective publicity campaign can both induce a widespread belief in quite erroneous or misleading ideas, and also cause not so much the rejection but the discounting of evidence. But only for a time. In the end, evidence wins through. Perhaps the tendency of the human mind to question everything is ultimately a very great protection. For it means that even if false ideas become current (e.g. that millions of animal experiments are done in the cosmetics industry, or that one cannot develop tolerance to or dependency on cannabis), once such ideas become in any sense orthodoxy, they become themselves subject to doubt and scrutiny. Then the evidence begins to make its mark. But there is, of course, a price, paid by the continuance of unnecessary ignorance, and the suffering of its victims.

EMPIRICAL AND A PRIORI THINKING

As the trajectory of a pharmacologist's life moves from the laboratory to the committee world and back again, inevitably patterns appear. One is the division between those who have done experiments and those who have not. It correlates closely with the division between those with an empirical habit of mind and those whose approach is a priori. I suspect it is what really underlies C. P. Snow's two cultures. Most of the time we inhabit both worlds, but sometimes one meets each mode of thought in all its purity.

The a priori mode of thought needs some defense, if one is writing for scientists, for it seems so absurd to the scientifically trained not to learn from experience all that one possibly can. But there is more to it than that. It is only too familiar a sight to find the conclusions drawn from some body of empirical

evidence being bitterly disputed. The onlooker soon appreciates the adage about "lies, damn lies, and statistics". If someone then says, in effect, that there are a limited number of possibilities, that all the outcomes can be envisaged (using imagination, intelligence, experience, and wide reading), and that simply by reflecting on these one can reach rational decisions, it can be attractive and cogent. The empiricist himself uses such methods in deciding if something is "plausible". (The weakness is that in fact all possible outcomes cannot be envisaged.) If the approach is combined with skill in presentation, a powerful a priori case can be built up. It is here that training in the humanities or in law is so powerful; for it is a training that takes a vast range of human experience as its raw material, and teaches how to think deeply and argue cogently about it. Yet, in the end, one must see it as dealing entirely with the given. The facts of a case simply serve, not to suggest further inquiry, but to identify the category of previous thought and analysis to be applied. It can then be quite a battle to get new evidence sought for or considered.

The experimenter has ultimately a different approach. He knows that there are still things not known, which are also not deducible, and that they are out there waiting to be discovered, by the method of deliberate experiment. That method is easy to write about, but not so easy to acquire. I reckon that I did not really learn what it was about until I had been at Hampstead for around six months. There seems to be a similar interval with my graduate students, before they move from making the observations they feel they "ought" to make, to trusting what they actually see with their own eyes and having the confidence to act on it. A little later comes the marvelous time when they actually make a discovery, however minute, of something that was not known before. It is then that the feeling for when something is proved or not proved begins to grow.

Philosophically, of course, some argue that nothing is ever proved. So let us put it a little more practically: that the empiricist learns that, with the right procedures, he can reach conclusions on which both he and others seem to be able to build, conclusions that are not dependent on his own prejudice, nor on his own powers of advocacy, but which remain true when the experiment is in the hands of others. At that moment, he joins the community of experimental scientists, a community spread over the world among his contemporaries, and reaching back in time through the centuries and forward into the future. We are not just of the same family as our colleagues of today, but also of Ehrlich and Dale and Cushny and Abel and Stephen Hales and Robert Hooke and Robert Boyle.

The lesson of the experimental method is not pain-free, for it is accompanied by repeated demonstrations of how wrong one's ideas had been, of one's experimental inadequacies, of one's stupidity in framing rational possibilities. But once learned, the reward is great. Today, relativism underlies a great deal of thinking; and it often seems fair and cautious to believe that there is no certain

answer to some question. Yet if that leads on to the conclusion that it is never possible to say whether or not this or that "is the case", the outlook is depressing indeed; for then force would be the only way to settle uncertain questions. But the experimenter who finds that he can confirm another person's findings, or has his own unexpected results verified in another laboratory, begins to have some confidence that there is a world where something objective exists, that movement forward in some sense, however modest, is possible.

The empiricist's danger may be that of too great an attachment to the latest evidence. But he should be an optimist; for he knows there is more to find, and in that finding, new opportunities are born.

SOME CONCLUSIONS

By the time one retires, any generalizations one might make are of small use. Looking back, I think it was only rarely that I actually took advice; example was a much commoner source of information. At the same time, there are a few points that, if asked, I like to hint at.

The first is the importance of keeping your nerve. There are always ups and downs; but there are always new and unexpected opportunities. My own career allowed me several opportunities to take the road that clearly suited me; and others have told me the same. So one can make mistaken choices, and yet have other chances. I think, too, that the saying is right that "the main difficulty is almost always muddle not malice". Conspiracy theory seems to me historically inaccurate in almost every case; and it can waste a lot of time and emotion.

A second point is the importance of "self-diagnosis", of discovering where your real interests and skills lie. It is not easy, for at the start one does not know the options, and once you are launched there are plenty of pressures from others to do this or that. One useful measure is to discover what your mind turns to when it is "free-coasting", i.e. when there are no pressures on it, nothing is expected of you, and you are even a little bored. A similar test is to recognize those activities where time seems to disappear. Charles Morgan puts it romantically in "The Judge's Story": "ask yourself in what work, what company, what loyalty your own voice is clear and in what muffled. By that answer rule your life". One's mind has a "grain", and it is better to work along it.

A third point is distinguishing between the various meanings of the superlative case of the adjective "good". One meaning is simply "very good". A second meaning is "the best". This has the interesting feature of being a function of the surroundings. The level is set by the competition. While competition may be a potent stimulus, it may also be virtually absent. The paradox may then arise of the "best" not even being particularly "good". This is the weakness of relying totally on the competitive impulse. Finally comes "the best possible", where both the competition and that internal impulse to do yet

better are both drawn upon. Here is where the new ground is broken. Wordsworth describes it, in his passage on the bust of Newton in King's College Chapel, as "the prism and silent face, the marble index of a mind voyaging through strange seas of thought alone." That level is for only a few, but perhaps L. W. Collison's notice in F4, mentioned earlier, "Near enough is not good enough", was in the same spirit.

Lastly, accuracy is a quality that can be most helpful. It need not be restricted to measurement. Sometimes a situation can get complicated, with allowances here, and compensating severity there. If one sets aside all the adjustments, and simply tries, at the start, to make as accurate a description or diagnosis or account as possible, it can release a cramp. Everyone respects accuracy; and once the initial ground is clear, solutions become easier to find. None of these matters are easy; but a strategy that seeks to begin with accuracy is off to a good start.

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