Henry H. Dale

PHARMACOLOGY DURING THE PAST SIXTY YEARS

By Henry H. Dale

52 Queen Anne Street, London, W.1., England

Having been invited to give a "popular" lecture to members and friends of the British Medical Assocaition attending its Annual Meeting in July 1948, I chose as my subject "Accident and Opportunism in Medical Research." Now, just 14 years later, as I prepare to respond to another flattering invitation, on this occasion to write a Prefatory Chapter for next year's (1963) Annual Review of Pharmacology, it occurs to me that my own connexion with pharmacology was the result of an unexpected opportunity, which I felt bound to accept, and not of any deliberate intention or planning of my own. And that, in keeping with this casual origin, nearly all the investigations in which I had the privilege thereafter to take part, during the period of nearly 40 years of activity which ended with my retirement, now 20 years ago, were concerned with problems or phenomena which were brought to my notice by requests, or encountered by accident while I was following such suggestions from others, and never with any plan of research which I had chosen for myself and consistently followed. I greatly admire those of my colleagues who have been able to select special research objectives for themselves, and to adhere to them pretty closely; but I have to recognize that my own scientific instinct has not had that kind of spontaneity, or tidiness; so that even the fact that people have been apt to regard me as a pharmacologist, has been the result of accident, rather than of my own intention.

It would hardly have been possible, indeed, for me to make a conscious choice of Pharamcology as the main subject of my future activities, at the time when my formal studies came to an end with my graduation, first in science and then in medicine. For I had not, so far, encountered pharmacology as a subject either of study or research, and had no basis for a judgement of the kind of interests and opportunities which it might offer. I had taken physiology and zoology as my principal subjects for the Cambridge Tripos examination in 1898; and then I stayed there for two further years, holding a post-graduation research studentship, and getting my first experience of research in physiology, under Professor Langley's guidance. Cambridge, however, had offered me no course in pharmacology; W. E. Dixon had not, I think, been appointed to start one there until after I had left for London, to complete the clinical stage of my medical curriculum at St. Bartholomew's Hospital. And, during those two further years, till 1902, I certainly received no encouragement to regard a career of study and research in pharmacology as a worthy object of ambition. I rather vaguely remember that we students had to obtain certificates of diligent attendance at a course of lectures in some subject of the kind; but these certainly amounted to no more than the perfunctory presentation, by one of the Assistant Physicians, of certain odds and ends of *materia medica* and toxicology.

As for research, the very distinguished and candid physician, in whose

wards I began my clinical studies, made it very clear to me that medicine, as he understood it and was prepared to teach it, was still a traditional art, an empirical craft; so that my first duty, on entering his wards, was to forget anything which I might have acquired, of physiology as an experimental science. And, indeed, what I learned of medicine and its practice in that all too brief experience, was not incompatible with that negative estimate of its connexion, at the beginning of the present century, with the knowledge which had so far been made available by the experimental methods of the laboratories. Successes like the thyroid treatment of myxoedema, or of diphtheria with the specific antitoxin, both of them then about ten years old, had, of course, been adopted; but there seemed to be little expectation of more to come. So, medicinal treatment was still very largely empirical and traditional, and the use of it varied widely with the temperaments and attitudes of different physicians. Some of them liked still to prescribe elaborate mixtures, of many drugs without any serious credentials, on the ground that they had "seen them do good"; while others restricted their treatments to the very few which had scientifically intelligible actions, and used these one at a time. Perhaps the most promising portent, if anybody could have interpreted it, of the coming revolution in pharmacology and therapeutics, then still some decades in the future, was the arrival of aspirin at the hospital while I was still a student. This was put forward, to be tried by one of the physicians, as just a synthetic derivative of salicylic acid, with the claim that its use in acute rheumatism would avoid the irritant action on the stomach, with which the large doses of unsubstituted salicylates were apt to complicate that treatment.

By 1902 I had to decide what to do next. Further and more responsible clinical experience, as a house-physician, was available for my acceptance. On the other hand, one of the very few studentships which then existed for the frugal support of a year or two of research, had just fallen vacant; and if it were awarded to me, I should be committing myself to the precarious prospect, of finding some entry into teaching and research in physiology, for my further support at the end of a two years' tenure. On balance, however, and following what seemed to be my more natural instinct, I applied for and was awarded this George Henry Lewes Studentship. It allowed me to base my activities for the next two years on the Physiological Department of University College London, by favour of Professor Starling, who then recently, in co-operation with his brother-in-law, Professor W. M. Bayliss, had been discovering there the control of pancreatic secretion by the hormone, Secretin. My efforts to extend the application of this discovery came to nothing of serious importance; but I had a further and first-rate opportunity of gaining experience of the methods used in mammalian physiology, and of making personal contacts with a number of research workers, dealing there with different aspects of it. Several of these encounters led to lasting and highly valued scientific friendships. And among these I should specially mention my first meeting there with Otto Loewi, who was then visiting Starling's department, and making shorter visits to Cambridge and to

Oxford, in order to familiarize himself with English methods and ideas in physiology and the related disciplines, his own career being then already committed to pharmacology. He and I formed a personal friendship then, which was to become closer with a new coincidence of our research interests some twenty years later, and to last till his death in New York, on Christmas Day, 1961.

It might be thought, perhaps, that I gave already some sign of a potential interest in pharmacology and experimental therapeutics, in a more general sense, when I used some four months of my tenure of the George Henry Lewes Studentship to take myself to the Institute für experimentelle Therapie, in Frankfurt a/M., with the idea of working for a time under the direct influence of Paul Ehrlich, whose methods and ideas seemed, even to my inexperience, to be among the most original and enterprising of any in the whole range of medical researches at that time. I was given a most friendly reception; and, even though Ehrlich's own devoted colleagues warned me that I could not expect to get anything done in so short a visit, and that it would hardly give me time to get used to Ehrlich's spasmodic and almost explosive methods of guidance in research, I do not doubt that I returned to London with my mind open to a wider range of possibilities, in experimental medicine as a whole. Ehrlich, while I was with him, had been in process of shifting the centre of his own interests, from immunology and his side-chain theory of its mechanism, to a closer concentration on the possibility of an artificial chemotherapy of infections, based upon his earlier interest in the selective staining properties of the synthetic dye-stuffs. And it is just possible that a rumour of the contacts which I had thus been making with new ideas in therapeutics, may have had some connexion with an offer which was made to me from an entirely unexpected quarter, not long after my return from Frankfurt. Henry S. Wellcome wished to find somebody who was prepared to undertake researches in pharmacology, in the Physiological Research Laboratories which he had established in connexion with the pharmaceutical business of Burroughs Wellcome and Company, of which he had become the sole proprietor through the early death of his partner, S. M. Burroughs. When I saw Mr. (later Sir Henry) Wellcome, I thought it proper to tell him that I had never heard a lecture, or read a textbook, on pharmacology; and that, in fact, I had nothing to offer, which seemed relevant to the appointment which he had in mind, beyond a certain experience of physiological techniques. I don't know whether he was more impressed by my candour or my impudence. In any case he offered me the appointment, at a salary which would make it possible for me to marry; and he did me the signal service of expressing the hope that, without disturbing any of my own plans for research, I might try, in due course, to do something about the pharmacology of ergot. I never discovered the source of his interest in that drug; perhaps some rival pharmaceutical enterprise was having success with a proprietary preparation of it. In any case, having accepted the opportunity which was offered, I decided that I had better have a look, at least, at the possibilities of ergot, as a subject for my first experience of research in pharmacology. This

was made much easier for me by finding that the late George Barger, an organic chemist of real distinction, whom I had already known slightly from Cambridge days, who was to become my intimate colleague under different auspices for some 12 years, and my close friend while he still lived, was already working in the Wellcome Laboratories. Barger engaged in some preliminary chemical studies of the preparations which had been described as "active principles" of ergot; so that he was ready to welcome cooperation from somebody qualified to examine their physiological activities.

I have already given elsewhere,[1] in a collection of some of my published researches with explanatory comments and details, an account of the series of accidents, which seemed almost to force successively upon my attention, during the 10 years which I spent at the Wellcome Laboratories, from 1904 to 1914, the clues to practically all my subjects of research while I was there, and then to most of those on which I was still to be engaged during my 28 years of further activity, at the National Institute for Medical Research, until my retirement in 1942. First came what, in the circumstances, might have been an almost disastrous blunder, which led me to recognize the remarkable "sympatholytic" and corresponding "adrenolytic" effects, produced by several of the preparations from ergot which I received from Barger. And this brought me into close and co-operative contact with another lifelong friend and colleague, the late T. R. Elliott, and with his brilliant proposal, published in 1904, of a chemical-transmission mechanism, to account for the closely sympathomimetic actions of adrenaline (epinephrine). And again, in studying this action of one of Barger's ergot preparations, in paralysing, or reversing, the augmentor actions of adrenaline and of sympathetic nerves, I used a dose of post-pituitary extract as a control pressor agent, showing that its action was unaffected by the ergot-paralysis. By sheer accident, I happened in that experiment to be recording the contractions of the uterus as well, and thus saw, for the first time, the stimulant effect of the post-pituitary extract on that organ, later shown to be due to a separate hormone, oxytocin.

Then we found that most of the watery ergot preparations, which were being used with apparent satisfaction in obstetrics, showed practically none of this sympatholytic action, now known to be due to the alkaloids, ergotoxine, ergotamine, etc. Further, we found that some of these extracts were being issued, for clinical use, as "standardized" by observing their vasopressor actions; and, yet again, from observations made by factory colleagues, that the preparation of such extracts was accompanied by evidence of extensive putrefaction. Barger and I were thus led to study the "sympathomimetic" activities of a series of simple, proteinogenous amines, leading, by stages of increasingly close similarity in structure, up to adrenaline and its immediate homologues.

Somewhat later, I saw a demonstration at an international Congress,

[1] *Adventures in Physiology, with excursions into autopharmacology.* Pergamon Press, Ltd., London, 1953.

suggesting the presence, in a particular kind of ergot extract, of another highly active amine, presumably a product of another kind of putrefaction; and Barger identified this as histamine, just as Ackermann, in Germany, had obtained the same substance by the deliberate putrefaction of pancreas. Thus emerged the relation of the actions of histamine to the long known action of "Witte's peptone," and to the then recently discovered symptoms of the anaphylactic reactions, as seen in different species. Again by accident, through the reprehensible supply to me of a horse-serum sensitized guinea-pig, for my experiments with isolated plain muscle, came new light on the mechanism of the anaphylactic shock. Studies of the part played by the release of tissue histamine in the anaphylactic reaction, and in allergic reactions in general, and in various other physiolological and pathogical reactions in different species, are still, of course, in vigorous progress in many laboratories and clinics all over the world, at a time when I am long past the possibility of participation. In these more recent years, histamine has even had a rival, as a speculative participant in these normal bodily functions of different species, in serotonin, the analogous amine from 5-hydroxy-tryptophane.

I suppose, however, that the most important of this series of clues, which seemed to be almost forced upon my notice, whenever I "tried to do something about the pharmacology of ergot," was the one which came to me towards the end of my 10 years in the Wellcome Laboratories. A particular batch of an ordinary ergot extract was found to have a very potent, vagus-like cardio-inhibitory action; and the constituent responsible for this, when it was isolated for me by my then colleage, the late A. J. Ewins, was found to be very unstable in watery solution, if the reaction were even weakly alkaline. The properties suggested a labile ester, and I naturally thought of acetylcholine, which had been made some years earlier by Dr. Taveau for my friend, the late Professor Reid Hunt, who had found that it was some thousands of times as active as choline, in inhibiting the beat of the heart. We soon established its identity with the active ester from the ergot extract; and experience then suggested to me that it might be worth-while to examine, in greater detail, the activities of anything which came to my notice from a preparation of ergot. As a result, I found that acetylcholine possessed two kinds of activity, which I described by their respective close resemblances to those of muscarine, easily paralysed by atropine, and those of nicotine, resistant to atropine, but paralysed by nicotine in large doses. In comparison with the actions of a series of other choline esters, the actions of acetylcholine seemed to be uniquely characterised by a combination of high intensity and rapid evanescence. The hypothesis of a chemical transmission of effects at neuro-effector junctions had originally been put forward to account for the intensely sympathomimetic and rapidly evanescent actions of adrenaline. And now on similar terms, its plausibility could be extended to account for the correspondingly parasympathomimetic actions of acetylcholine, and even, perhaps, for its "nicotine" actions at ganglionic synapses and "voluntary" neuro-muscular junctions. Two possible candidates for the

hypothetical transmitter-functions, at these different junctions, were thus now in view. Nothing more, however, could be done about it, until somebody could produce direct, experimental evidence of the liberation of such transmitters; and of this there seemed to be no prospect.

When the outbreak of the first World War occurred, I had undertaken a new position under the (British) Medical Research Council, and diverted all my research energies, to meet all kinds of unfamiliar emergencies. And when the War had come to an end, there were still some years required to deal with its aftermath, and before I could be re-accommodated in my new quarters. Then, just as this transfer had been completed, the chemical transmission hypothesis was suddenly promoted to the status of an experimentally demonstrated fact, when my old friend, the late Otto Loewi, published a description of his brilliant demonstration on the isolated hearts of frogs. His results were only the more convincing, because of the elegant simplicity of the experimental technique. Loewi had demonstrated the liberation, by the stimulation of the vagus and the sympathetic nerve supplies to the heart, of the two correspondingly active transmitters; and only a few years of more detailed experimental work were needed to identify these, in the one case as acetylcholine, and, in the other, as adrenaline, or its primary nor-homologue. So that Loewi's now classical demonstration had, in fact, provided a new and realistic starting point for all the further extension, still in progress, of physiological and pharmacological knowledge in this field.

I hope that, in writing so much about my personal experience, and about the clues which ergot had seemed almost to thrust at me, I shall not be suspected of assuming that even all the new advances of knowledge in physiology and pharmacology which have resulted from the researches of all those who have followed one or another of these clues further, and to deeper issues, and largely in the twenty years since my own retirement, have together made more than a limited and specialist contribution, to the tremendous transformation and extension of pharmacology and medicinal therapeutics, since the end of my student days, now 60 years ago.

In a chapter such as this, however, it would be impossible to attempt more than a mere mention, of some of the main sources of new experimental knowledge, through which this revolution in the therapeutic position and prospect has been brought about. Biochemistry, in any worthy sense, was still an academic novelty at the end of the nineteenth century, and the recognition and practical application of the vitamins was still at an early stage, when the first World War began, in 1914. Which of us, in those days, could have foreseen the extent to which biochemical knowledge and methods would, by now, have permeated already into almost every aspect of medical activity, in experimental laboratories and clinical wards alike? The application of endocrinology also, to practical therapeutics, seemed earlier to have come almost to a standstill, during the three decades which followed Murray's first use of thyroid gland in myxoedema, in 1891. Then in 1921, the same year as that of Loewi's demonstration of chemical transmission—a vintage year, surely—came Banting and Best's discovery of insulin. And this not only produced the first and rapidly successful treatment of a rela-

tively common and distressing endocrine deficiency, but, therewith, gave immense encouragement to new endocrinological research and enterprise. The result of this was that, during the next few decades, the whole field of the hormones of the adenohypophysis, the adrenal cortex, and the gonads, and of the complex interrelationships of their actions, became widely opened to successful investigation, with results of the greatest importance to normal and morbid physiology, and then to practical therapeutics. In medicine the uses of both vitamins and hormones have, of course, a common character, in that both are concerned with correcting specific deficiencies of substances required for the maintenance of normal activity, growth or, more generally, of normal metabolism. These deficiencies occur in the diet in the one case, and in the body's own endocrine output in the other, and it is evident that, in one instance at least, there has been some theoretical overlap between the characters attributable respectively to a vitamin and a hormone. The erthropoietic principle, with its remarkable cobalt-containing structure, which Minot and Murphy first extracted from normal liver substance, might, perhaps, have been expected to be classified as a hormone, by analogy with thyroxine and the rest; whereas, presumably by reason of some feature of its chemical character, it has been authoritatively included in the vitamin series, as Vitamin B_{12}. The central position which both vitamins and hormones have now come to occupy in therapeutics, and in pharmacology as its experimental basis, has, in any case, been the result of research developments during the past three or four decades.

Much the same might be said of the development of another major contribution to the recent immense expansion of the resources available to therapeutics, aimed, in this case, not at the correction of deficiencies, but at the prevention or removal of detrimental infections, by artificial remedies specifically toxic to the invaders. In spite of the resounding triumph scored by Ehrlich's chemotherapy, with his introduction of arsphenamine (Salvarsan), for the effective treatment of syphilis and other spirochaetal infections, it seemed to be widely assumed during a period of more than twenty years which followed this discovery, that, while more of such artificial, synthetic remedies were likely to be found for the specific treatment of zoological or spirochaetal infections, only natural, immunological methods were worthy of further investigation, for the prevention, control, or cure of the commoner diseases due to bacteria. And then, almost suddenly, from 1935 onwards, through the discovery and progressive introduction, first, of the synthetic remedies of the sulphonamide series, and later, during the second World War of methods for the purification and mass-production of Fleming's penicillin, and later of a still expanding series of specifically active antibiotics, the whole aspect of the prevention and treatment of a great range of the bacterial infections has been rapidly transformed. Thus, another great chapter has been added to the volume which deals with the interests and responsibilities of pharmacology.

Meanwhile, during the last four decades, a whole new range of infective agents has come clearly into view, in what were formerly known as the invisible, sub-microscopic, or ultra-microscopic viruses; though only the last

of these terms is now suitably applicable to them, in the sense that most of them have now been actually brought into view, but only by the comparatively recent introduction of the electronic ultra-microscope. At present, they too, are in the position that, while methods are available for preventive immunisation against their infective activity, methods for the direct treatment, of an infection which has already gained an effective hold in the patient, are not yet clearly in view. Experience, however, would surely recommend hesitation, before even any provisional assumption is allowed to take root, which would exclude the possibility that an artificial chemotherapy, even of such virus infections, may yet become available.

So far I have been discussing methods of treatment which, though they figure so prominently in therapeutic practice at the present day, would hardly have been recognized, by the pharmacology which existed at the turn of the century, as coming within the purview of its special aims and activities. And I suppose that these newer therapeutic methods may have come the more readily to my mind, in writing this chapter, because it has been my privilege, in the case of a good proportion of them, to make touch with their development, not as a participant in their discovery or investigation, but through official concern with the methods required for their standardisation, or with the conditions required for their clinical trial with adequately scientific controls. I am, of course, aware, on the other hand, that, mainly since my own retirement from any kind of active concern with such developments, there has been an almost explosive output of new remedies, of types which more nearly recall some of those which were in use with no more than traditional sanctions. I am also aware that the essential aims of this swelling flood of new remedies is the amelioration, or suppression, of symptoms, rather than the prevention, or elimination, of causes. They differ, of course, and very fundamentally, from the old traditional nostrums, in that their discovery and introduction have been based on knowledge and theories of the methods of drug action, which have only been made possible by the essentially modern developments of all the contiguous scientific disciplines—physiology, experimental, pathology, biochemistry, even biophysics. For pharmacological researches and theories, as these *Annual Reviews* are making abundantly manifest, are now delving ever more deeply into more fundamental layers of scientific knowledge; the activities of these symptomatic drugs are interpreted ever more in terms of their actions on enzymes, of their own liability to enzymatic change and destruction, and of other basic conceptions of biochemistry and physiology. These things seem to me to be opening ever more hopeful vistas of the progress of essentially pharmacological knowledge by research. On the other hand, from the point of view of one who has had practically no personal experience of the educational problem, I cannot help wondering how those responsible for the teaching of pharmacology to the students, are now going to select their material for a course which will meet the educational and practical needs of the doctors of today, and of the immediate future, from the almost overwhelming torrent of detailed knowledge which now challenges their attention.

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