A modification of receptor theory

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Commentary by

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When I entered pharmacology in the 1940s, there was little discussion of theoretical ideas about the action of drugs; that I became interested in such notions probably derives from my having a different basic training from that of most pharmacologist.

I was an undergraduate student of chemistry at Birmingham University in the latter years of the Second World War. At this time, chemistry was one of the few disciplines which permitted a student to have military service deferred. But we had to undertake military training on two afternoons each week during term and to attend a fortnight's camp in the summer - following an extra six-week 'term' in what would otherwise have been the summer vacation. The male undergraduates formed a battalion of the Home Guard charged with the defence of a segment of the periphery of Birmingham: a youthful version of 'Dad's Army'.

One research group in the Chemistry Department received funding from a quango called the Colonial Products Research Council (later, Corporation). Someone had pointed out that the chemical industry was wholly dependent for its starting materials on coal tar. To the question of what would happen to chemistry when coal reserves were exhausted, the answer came that the coal could be replaced by a renewable resource, cane sugar, whose molecules contain a backbone of carbon atoms. The Chemistry Department's research group was therefore investigating ways of using cane sugar as a starting point for chemical synthesis in general, and, in particular, the possibility of synthesising substitutes for aspirin, the exemplar of a pharmaceutical derived from coal tar. When the group had synthesised a number of compounds, Professor W.N. Haworth wrote to J.H. Burn, Professor of Pharmacology at Oxford, to ask if he could have them tested to see if they were active. Burn replied that no-one was available to carry out the tests, so Haworth suggested that one of his students who was about to graduate could be funded by the C.P.R.C. to go to Oxford for the purpose. And that, in outline, is how I became a pharmacologist.

At that time, there were few Departments of Pharmacology in the universities; in most, pharmacology was taught to medical students by a lecturer or senior lecturer in the Physiology Department. The main exceptions were University College London, Cambridge, Oxford, and Edinburgh where Materia Medica had become a laboratory discipline rather than remaining a clinical one, as it was at the other Scottish Medical Schools. Pharmacologists were almost exclusively medical graduates, but the Oxford Department of Pharmacology was unusual in that, in addition to the medically qualified pharmacologists, a distinguished biochemist, H. Blaschko, and a distinguished chemist, H. Ing, had been imported by Burn. However, they remained biochemist and chemist, respectively, albeit with an interest in drugs. Here was I, a newly graduated chemist, faced with gory experiments going on around me while I stuck clinical thermometers into rats' rectums every ten minutes for two or three hours (the antipyretic action of aspirin was measurable, but not the analgesic action). Burn was unsure about how an uncouth chemist would fare in the medical world of pharmacology. He thought that a career as a technician might be the best I could hope for, so he sent me to the animal house for my first two weeks. However, after I had served for a year with the clinical thermometers, he was pleased enough with me to decide that I should have a more general pharmacological training, and asked W.N. Haworth to provide another chemistry graduate to continue the good work on antipyretic action. Thus John Vane, too, became a pharmacologist - and his interest in aspirin-like drugs was to prove more persistent than mine!

Although it had no relevance to my investiga-

tion of some obscure alkaloids, I came across Clarke's idea of applying the law of mass action to drug action - what a discovery that was in the sea of empiricism that constituted just about all of pharmacology! It seemed almost too good to be true, as I later discovered it was. I also at some point came across the paper by Trevan and Boock (1927) in which they investigated the effect of pH on the action of local anaesthetics and concluded that it was the free base, not the ion, which was active. (Much later investigation by others claimed that it was access to the site of action that required the base (Ritchie *et al.*, 1965)). This, again, was something that a chemist could appreciate.

When I was appointed as a research assistant to H. Heller in Bristol, I had some time to pursue my own research. I decided to try to do for histamine what Trevan and Boock had done for local anaesthetics. I did not know how a piece of guinea-pig ileum would behave at different pHs, but it seemed worth testing, and as a control there was acetylcholine whose state would be unaffected by changing the pH. I enrolled as a PhD student with that as my subject. Using borate buffers to modify Locke's solution, I found that ileum worked reasonably well unless one changed the pH too often. But there seemed to be no change in the relative activity of histamine to acetylcholine with a change of pH, which I found puzzling. At about this time, Gaddum offered me a lecturer's job at Edinburgh, which, of course, I accepted. The move disrupted the histamine investigation and I allowed the PhD registration to lapse. I continued to worry about histamine, thinking that, because the concentration of ion and base changed with pH but the activity of histamine did not change, perhaps the answer was that the receptor was vulnerable to pH change and dissociated in a way that compensated for the change in histamine. At the time, there was much interest in the newly-discovered antihistamines (later to become known as H_1 receptor antagonists). These were shown to be competitive antagonists of histamine, so that, if antagonists with a range of different dissociation constants could be obtained, they might be expected to behave sufficiently differently with a change of pH that my hypothetically dissociating receptor would be revealed. However, the complexity of the experiments and the uncertainty about the outcome made me reluctant to embark once more on a PhD with the study of this problem as its subject. Casting around for an alternative, I came to the idea that started this paper.

I am now not clear which of the ideas that are presented in the paper came to me first. It reads as if doubts about the shape of the dose response curve started me off, and that is probably how it was. I remember telling Gaddum at some point that the frog rectus contractions induced by carbachol were very different from those induced by acetylcholine, and that the difference was obviously due to the action of cholinesterase. He chided me for jumping to conclusions, but I thought that it was so obvious that it was scarcely worth doing experiments with an anticholinesterase. So he wagered me (a predecimal) sixpence (2.5 pence) that the anticholinesterase would not make acetylcholine behave like carbachol. I showed that it did, but never received the sixpence. I also recall how surprised Gaddum was when I pointed out that the slope of adrenaline contraction of rabbit uterus from his 1926 paper was much too steep to fit the mass action curve. He, like everyone else, had been persuaded by Clarke.

I discussed some of the ideas in the paper at meetings of the British Pharmacological Society. I do not remember much of the ensuing comments, except that one member complained bitterly that my discussion was as futile as the medieval dissertations about the number of angels who could dance on the head of a pin. I was grateful when Trevan spoke in my defence.

I found great difficulty in actually writing the paper. Gaddum liked the early drafts, which he found tough going, and doubtless made me rewrite several times. After much discussion, when we were both satisfied, the paper was submitted. At a meeting of the Society, Trevan told me that he had been asked to act as editor, and asked if we could discuss the paper. He said that, while it interested him, it was only at the end that he began to understand it. I had tried to save the discussion for the end, as a conclusion drawn from the evidence presented. Trevan insisted that the conclusion should come quite early in the paper, otherwise readers would not be able to understand and would probably give up. Although I thought this rather unscientific, I agreed; I certainly did not want readers to give up.

I do not know how much impact the paper had, although I know that it has been widely read: in copies in several libraries, there is a visible vertical black line in volume 11 of the British Journal of Pharmacology where pages 379-393 have been much fingered. Jim Black tells me that he found it useful when developing ß-blockers, and David Jack once told me that he instructed new recruits to

Glaxo research that it was the most important paper published this century. But, for many years, there seemed to be few published discussions of drug action which took in the changes I had proposed.

Now the scene has changed decisively. 'Receptors' have long been isolated and probed. I was a little saddened by the way in which the whole complex of polypeptide molecules, which form channels through membranes, have been called receptors. For me, the receptor is that grouping of the atoms, whether on one molecule or several, with which the agonist molecule links to initiate the change of conformation which results in the effect characteristic of the agonist.

References

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