RECEPTORS AND THE CHEMIST
DICK BARLOW

Did you ever meet A J Clark, the man who really put receptors on the map?
I never met A J CLark but my supervisor, H R – Raymond - Ing, knew him well and really appreciated him. Ing was a chemist working in Professor Burn's laboratory. He started a course in Pharmacology as a supplementary subject for honours chemistry students in 1945. I was one of his first students. The other was Michael Grundon who later became professor of chemistry at the University of Coleraine. Ing's lectures were superb, fascinating for a chemist, showing the uses of chemistry in developing drugs. Professor Burn's practical class was equally brilliant - he had excellent demonstrators - so we not only heard about things, we had a chance to do relevant experiments ourselves. That's what got me started because I then went on and did my research year - Chemistry part II - with Ing, making compounds and testing them.

Clark's ideas about receptors were an important feature of Ing's lectures. The Langmuir adsorption isotherm and Michaelis-Menten theory were very much part of thought at that time and you can get some idea of the background from a book I wrote when I was in Glasgow. This is really a large section of Ing's lectures. I wrote it with his approval. I don't think he would have produced it himself, he was a perfectionist whereas I was young and brash. For the chemist the argument about receptors really goes back earlier to the work of Cushny on the difference between the isomers of atropine. This compound was important because it was used by Dale to block the muscarine-like effects of acetylcholine but it is a mixture of two enantiomers, (+) and (-) hyoscyamine, and Cushny found that the (-) form was very much more active. These molecules differ only in their arrangement in space so whatever they are doing to produce their effects must involve some 3-dimensional structure - a receptor.

I believe physiologists thought differently and Sir Henry Dale was careful to refer to the "muscarine-like" or "nicotine-like" actions of acetylcholine. Perhaps they were less familiar with the chemical evidence from stereo-specificty. Even today some people seem to need reminding that atropine is a racemic mixture. Their argument was that you shouldn't multiply your hypotheses unnecessarily - Occam's razor. I think this ended in the 1970s when you had radio-labelled drugs sticking to cell fragments, but even then there was still the feeling - with some reason - that these binding sites may not be the same as receptors in functional cells.

Did you ever meet Henry Dale?
I have only heard him talk. At one time he came to meetings of the British Pharmacological Society and he was a bit of a terror for young pharmacologists. He could appear to be asleep and then wake up and ask awkward questions. I wouldn't have dreamt of asking him if he really believed in receptors. It wouldn't have worried me if he didn't.

He was also associated with the electrical versus chemical neurotransmission story. While he was prepared to accept that ACh was a neurotransmitter in the periphery, he was much less willing to be persuaded that this was true in the

brain. And it seemed that even as late as 1960 very few of that group - Dale, Vogt and Gaddum - were really convinced that there were neurotransmitters in the brain.

I know Dale's work mostly from the collection of his papers which appeared as "Adventures in Physiology" in about 1960. I don't know what Gaddum and Vogt thought about transmission in the brain even though I joined the Edinburgh department in 1955. Gaddum had collaborated with chemists from Glaxo in looking for compounds which antagonised the effects of 5HT when tested on the isolated rat uterus. He was particularly struck by the activity of 5-benzyloxygramine, which has only one methylene group in the side chain attached to the indole nucleus, and wanted to test 5-benzyloxytryptamine but the Glaxo group was more interested in harmane derivatives. In 1949, after finishing a DPhil under Ing, I had moved to Glasgow as an ICI research fellow in the Chemistry department but I kept in touch with the Oxford department sending them compounds to test. Burn and Ing had arranged that I should go to Arnold Welch's department at Yale for the year 1954-55. I had been offered a job in Glasgow and wrote to Ing for advice about whether to take it up and he suggested I go across to Edinburgh and consult Gaddum, "because he will know the local conditions better than I do". I went to Edinburgh and Gaddum suprised me very much by asking me whether I would join his department. So I went off to Yale for a year knowing that I had a job in Edinburgh to come back to. That doesn't answer your question about Gaddum's ideas about transmission in the brain but he undoubtedly believed that 5HT was involved in some way.

Was it called 5HT rather than serotonin at this point?

People around me referred to 5HT. I was aware that serotonin was another name for the same compound based on what it did and how it came to be discovered. Once you knew what it was it seemed "right" to me to use the chemical name but I think this may have been a British attitude and people elsewhere continued to use serotonin. There seemed to be a general idea that levels of 5HT were linked with mental illness - too much produced depression and too little produced schizophrenia. This was why you went mad with LSD, which antagonised 5HT.

Tell me about the work on 5HT antagonists

I made series of analogues of tryptamine and 5HT with the general idea that as you increased the size of groups, on the side-chain nitrogen, for instance, you might pass from agonists to antagonists. The pharmacological testing was mostly done by Inayat Khan, from Pakistan, who had come as a British Council Fellow to be trained in pharmacology. The testing was all on isolated tissues set up in an organ bath and at the start he used the isolated rat uterus preparation as before. John Vane, meanwhile, had described the rat fundus preparation and Inayat went off to learn the technique and most of the testing was done on this preparation. We also used the guinea-pig ileum. The results are described in three papers, which overlap papers by John Vane who was testing similar compounds which had been made by ICI.

I had met John Vane in Burn's department, where he succeeded R.P.Stephenson as a B.Sc. student. He was in also Welch's department at Yale from 1953-1955. He had been there for a year before I arrived and was extremely kind in helping me to settle down. We even worked together on sulphonium analogues of

hexamethonium as ganglion-blocking agents. He then returned to join Bill Paton's new department at the Royal College of Surgeons, London.

When you are looking at things like the rat uterus and rat fundus, you are assuming that you're acting on a receptor there.
Yes. When you came from the chemical side it seemed obvious. I've mentioned stereospecificity already: I should have added the important influence of developments in chemotherapy which were well presented in Adrien Albert's little book in 1946 "Selective Toxicity". This was soon followed by Work & Work's "The Basis of Chemotherapy". The idea of receptors was an accepted part of chemotherapy, arising from Ehrlich's work, and the antimetabolite approach to chemotherapy, following the discovery of the mechanism of action of the sulphonamides, was well established. Pharmacology was then closely allied to chemotherapy, which was about half Ing's course and the title of the new publication, of which he was the first editor, was the British Journal of Pharmacology and Chemotherapy. Perhaps I don't know enough physiology to appreciate the difficulties, which some people had, but I still find odd that the idea, which originally came from Langley's work with nicotine in the 19th century, should have been such an intellectual problem.

How much of this hypothetical entity argument did you meet at meetings?
You had to be careful. With friends you talked about receptors but there was always the feeling that your seniors would disapprove. After all, your reasons were usually based on the effects of antagonists and the possibility that you might be able to isolate a receptor seemed very remote. You had to be particularly careful in what you wrote for publication.

So you had putative receptors?
Yes.

What was the atmosphere like in the lab at that time. There was Gaddum, yourself, Stephenson...?
Marthe Vogt, Henry Adam and Tom Crawford. Gaddum was Professor and Marthe Vogt was Reader. Both had medical qualifications - Gaddum was also a mathematician - and both were Fellows of the Royal Society. They really knew their stuff and had international reputations. I respected them and was well aware that they were intellectually on a far higher plane than I was. When I joined the department Gaddum was doing a lot of travelling round the world, which is partly why I got involved in working out with Inayat Khan how our compounds were to be tested. Marthe Vogt was a brilliant experimentalist as well as very knowledgeable. She was also very kind, though some people were a bit frightened by her intelligence and high standards. She was one of the many refugees from the Nazis who did so much for pharmacology in Britain. Gaddum resigned the chair in 1958 and moved to the Institute of Animal Physiology at Babraham, near Cambridge, and Marthe Vogt joined him there a year later. This should have allowed him longer before he had to retire but sadly he died not very long after leaving Edinburgh.

Henry Adam was also Reader and had a medical background. He had been in the department when A J Clark was Professor and worked with Gaddum on chemical

defence during the war. He was very interested in histamine and had done some elegant work on its distribution. I had already met him at Yale where he was on an exchange visit at the same time as I was. He later succeeded Ing as editor of the British Journal of Pharmacology. Tom Crawford had come from the Edinburgh biochemistry department to help with the measurement of catecholamines. Before the development of fluorimetric methods these all had to be measured by bioassay. You measured adrenaline with the rat uterus and noradrenaline plus adrenaline on the rat blood-pressure and worked out the noradrenaline by subtraction. Crawford was magnificent at this kind of work and organized a superb set of practicals for medical students in which I was allowed to help. In those days medical and dental students had a course of ten experiments and I learnt a lot from them. Crawford was painstaking in making sure they all worked. I should also mention the head technician, N.E.Condon, who had started as a boy working at University College, London, before the first world war and came to Edinburgh with Cushny. He had an immense fund of stories about Cushny and Clark and he was brilliant at inventing gadgets, some of which may still be in use. There were 3 or 4 technicians and overall the departmental tradition was that sloppy experiments were unforgiveable. You had to be able to trust your results.

How much do methods drive the field, rather than the other way round?
Methods drive the field a lot. The advances I have seen are quite amazing. In the old days you relied extensively on analysis by biological means, bioassay. Burn's book "Biological Standardisation" was concerned largely with substances such as digitalis and hormones whose standardisation was essential for their clinical use. The Health Organization of the League of Nations very successfully produced international standards in this area. Of course these have been replaced by chemical methods and it is astonishing what can now be done in the way of analyzing unbelievably small amounts of material. I think, however, that something is lost when the term bioassay is used, as it seems to be nowadays, simply to describe biological testing. There is an important difference between comparing the effects of different concentrations of the same drug, which is bioassay, and comparing the effects of different drugs.

There is the danger that some work may be done simply because you have a new method but there have been situations where you can't get any further with existing methods and someone develops a totally new idea - the automation of experiments, introduction of micro-electrodes, patch-clamping, genetic engineering, new synthetic agents such as metal hydrides - and "whoosh" - you get a whole cascade of new findings.

How long had Gaddum been in Edinburgh before you went there?
Clark died in 1941 and Gaddum was appointed in 1942. There was no overlap. Clark had succeeded Cushny in 1926 but he was still quite young and died of a surgical complication which nowadays he wouldn't have done. I was at the BPS meeting in Edinburgh in summer 1948 and Gaddum and the department seemed as much part of Edinburgh as Arthur's Seat.

Gaddum didn't train there?
No. Gaddum was a Cambridge graduate. He was working on chemical defence during the war and in particular on arsenicals, such as Lewisite - chloro-vinyl dichlorarsine. He was involved in the development of British Anti-Lewisite (BAL) - dimercaprol. The name usually associated with this compound is Peters, Professor of Biochemistry at Oxford, but the mechanism by which it works, providing a source of -SH groups for the arsenic to combine with, gives you antagonism by neutralization Gaddum worked on and later included in an article in Pharmacological Reviews. Some work was done in a greenhouse on the roof of the department in Edinburgh. After the war I think the greenhouse found its way to Condon's garden. The remaining samples of poison gases were an embarassment and it was my job as the chemist to arrange for their removal. Someone from Porton Down eventually came and took them in their car for their museum.

What was Gaddum like? You said he was on a higher plane intellectually -
I intensely respected his intelligence. He knew things and at that stage I was quite prepared to respect people who knew things. He was a cheerful person. When Henry Adam and I were having a long chat about balances one day he said something like "Do stop it, you're like a couple of old women discussing hats!" Fair enough - though you couldn't say that today. I felt that he trusted me in chemical matters and wasn't going to interfere, which was rewarding. I didn't see much of him socially but I had a young family and his was grown up. I don't know how good an administrator he was but he found me a lectureship and money for setting up the chemistry lab virtually without my having to do anything. I was free to get on with the work, a very privileged position.

The impact of LSD on all this was fairly significant -
Yes. The story I heard was that - this was before my time - Gaddum had taken LSD and been out of his mind for 48 hours, much to everyone's alarm. There was the idea that in LSD you have as it were a locked 5HT molecule, which always struck me as a bit fanciful. There was no question, however, that it was active in very low concentrations and that it wasn't a competitive antagonist.

But LSD led to the idea that there must be a 5HT receptor and the claim that 5HT was involved trying to keep us sane in some way -
I can really only speak for the peripheral side. For a time I had Zuleika Picarelli as my neighbour in the lab on one side of me, with R P Stephenson on the other, so I could not fail to be aware of the discovery of 2 types of 5HT receptor. The original classification, using morphine and dibenyline gave the classification M and D and it was unfortunate that the official name of the latter was changed to phenoxybenzamine.

Would that have been one of the first times that anyone had actually distinguished 2 different receptors for a putative neurotransmitter, other than Ahlquist with alpha and beta adrenoceptors?
No, you had the division between nicotinic and muscarinic receptors and within nicotinic receptors a division between neuroumuscular- and ganglion- blocking agents. The idea that there might be subtypes of receptors wasn't totally strange but I think the general ruling was that receptors were the same until proved different

and this wasn't always easy unless you had selective antagonists. We found differences between analogues of tryptamine and analogues of 5HT which Vane had suggested were due to differences in their susceptibility to amine oxidase. I made experiments with some of the compounds and amine oxidase from guinea-pig liver and rat fundus and concluded that the "differential character of the blocking action of these compounds should be ascribed either to interference with the transport of tryptamine but not 5-hydroxytryptamine through the cell wall .....or to the existence of separate tryptamine and 5-hydroxytryptamine receptors. The amine oxidases ... appear to be a mixture of at least two types of enzyme, one of which has a higher affinity for 5-hydroxytryptamine and the other is more susceptible to inhibition by 2-methyldimethyl-tryptamine." But that was the end of my work in this field.

Did you ever meet the man who later put MAO-A and -B on the map - J P Johnson? Not even people who were in the area seem to know what J and P stand for -

I think I must have done much later but not at that time. This particular work was dying. Gaddum had left, Inayat Khan had obtained his PhD and moved to WHO at Geneva and the new Professor, Walter Perry brought new ideas and new staff, notably Walter Brocklehurst and Bernard Ginsborg. Walter was keen to put pharmacology on the map as a science subject. As at some other Scottish universities, you could get an honours BSc degree in pharmacology but few students took the course. They sat in on the medical lectures and had their own practical class once a week, which was organised by Marthe Vogt. Walter changed all this and arranged that students doing pharmacology should also do physiology and vice versa so that instead of perhaps 2 students every other year, we had a class of 10 or 11 consisting of science students and medical or veterinary students, taking a 1 year honours course.

At this time there was money and the students had a lab to themselves, newly equipped with, among other things, automated apparatus made by Stephenson for doing dose-ratio experiments. This equipment and its successors was used extensively all the rest of my time in Edinburgh because, at Stephenson's suggestion, we embarked on making parallel series of agonists and antagonists acting at muscarinic receptors in guinea-pig ileum. The ideas was we measured the affinity constants of the antagonists and hoped that this would indicate what would happen affinity when the same chemical change was made in the agonist series and from the activity of the agonists we might then be able to see how the change had affected efficacy. We were very lucky in having Ken Scott making the compounds and testing them. He had been a chemist at T & H Smith in Edinburgh and then joined the staff of the Herriot-Watt Technical College but wanted to do a PhD and his teaching duties didn't leave him any time for research.

Stephenson was there before you came to Edinburgh -

Yes. But I had met him in Burn's lab at Oxford. He read chemistry at Birmingham. At that time, during the war, Burn was very concerned about training suitable people to take up pharmacology and he had found money to take on a student to do a BSc at Oxford in pharmacology. This was a research degree, taking two years, and I was then doing chemistry part II. His successor was John Vane. Stephenson went to Bristol and was then recruited by Gaddum and started his well-known work on

receptors. I was then in Glasgow and made the compounds which he needed. He was very helpful in ordering equipment for my chemistry lab in Edinburgh while I was at Yale.

Why the ileum?
Nice, rapid responses. It's usually a quiet preparation, unlike rabbit gut, and lasts well. You can design experiments which can be done in a reasonable day's work. We used to reckon the guinea-pig ileum was student-proof.

Where did the Lock and Key idea come into the receptor story?
This was an accepted explanation of enzyme action. Are receptors just undiscovered enzymes? If they were, the response should be proportional to the concentration of enzyme-substrate complex and you would have a maximum effect when the enzyme was saturated. What Stephenson did was to question this assumption and show that with tissues, such as the guinea-pig ileum, it looked as if some drugs produced a maximum effect when only a small proportion of the receptors was activated. A J Clark had considered the implications of assuming responses were directly proportional to receptor occupancy. If this were true then the concentration producing a half-maximum response would be the dissociation constant. He went on to say that he thought this highly unlikely but this didn't stop some people thinking that if a compound was highly active it must fit the receptor well - i.e. have high affinity.

Stephenson suggested that compounds differed in their ability to activate receptors, differed in their efficacy, and that active agonists might produce a maximum response from the tissue with perhaps less than 5% of the receptors occupied. Nickerson showed this with histamine and ileum using an irreversible blocking agent. Ariens and his colleagues at Nijmegen had also distinguished between binding to receptors and activating them - their intrinsic activity - but assumed, at first at least, that all compounds which produced a maximum response from the tissue had the same intrinsic activity, i.e. the maximum depended on saturation. Stephenson's definition of efficacy assigned a value of 1 to a compound whose maximum effect was half that of which the tissue was capable, so highly active agonists might have efficacies of 10 or more. Such compounds lead to the idea that there are "spare receptors" which caused problems with some people. Indeed it's much simpler to believe that activity depends on fitting the receptor and this is what finds its way into some textbooks. It just happens to be wrong.

What role did Paton play in all this?
Paton's rate theory came five years later. I met Paton when I was working under Ing on bis-onium salts for Chemistry Part II. In the last century, Crum Brown and Fraser had found that the quaternary (metho-) salts of a wide variety of alkaloids all produced paralysis in frogs, apparently an action like that of curare alkaloids. They later showed that quite simple quaternary salts, such as tetramethylammonium, had similar effects and Ing suggested that for my part II, I should make some simple polymethylene bis-onium salts. These are salts in which two onium groups are present in one molecule as was believed to occur in (+)tubocurarine chloride. The idea was to test them on the rat phrenic-nerve diaphragm preparation which Dr Bulbring had just invented. At this time curare was coming into use as a relaxant in

surgery and in ECT. Pure crystalline (+)tubocurarine chloride was expensive and in short supply and crude extracts of curare alkaloids were used but required biological standardisation.

I was working away making these things and testing them after a fashion when Raymond Ing came back from a Physiological Society Meeting at which Eleanor Zaimis told him that they had also been testing these compounds and found them very powerful. Eleanor Zaimis was a British Council scholar working with Bill Paton at the National Institute for Medical Research in Hampstead and their work had started from the histamine-releasing properties of diamines, such as decamethylene diamine. They wondered whether quaternary salts behaved similarly. I think the compounds were made at the Institute by their chemist, Harold King. When the octamethylene compound was tested on the blood-pressure of an anaesthetised cat it stopped breathing and Bill Paton spotted that he was dealing with a potent neuromuscular blocking agent. In our tests on the rat diaphragm this compound wasn't particularly exciting and Raymond and I went to talk things over at Hampstead. There is a surprising difference in the sensitivity of different species to these compounds, as it turns out. Cats are about 100 times as sensitive as rats and mice with rabbits and humans closer to cats. We had been working with the wrong species. Burn arranged for Dr N K Dutta to test some of our compounds in rabbits and confirmed that the compounds were active, so we wrote the work up at this point and Paton and Zaimis carried on with further work, which included clinical tests.

The decamethylene compound, Decamethonium, was used clinically for a while but it became clear that although it produced paralysis it wasn't acting like (+)tubocurarine chloride. It was an agonist, not an antagonist, but its effects on the neuromuscular junction lead to desensitization. You could see that it was an agonist because it produced a contracture of muscles containing slow fibres such as occur in the neck of the chick. Bernard Ginsborg in Edinburgh actually found a muscle - the biventer cervicis - which contains both slow and twitch fibres so you could actually see both effects at once.

Paton was clearly puzzled by the idea that an agonist could produce a block and suggested that it was the rate of formation of drug-receptor complex which mattered, rather than the concentration of complex. As you approach saturation the rate falls off so perhaps this was why the effects decline. The problem is to design experiments to test this and the idea doesn't seem to be an improvement on the scheme of receptor desensitization which had already been put forward by Katz and Thesleff.

This brings us back to receptor theory circa the 1960s. You've got the Dutch, Edinburgh, some people in London. Were there any other world players?
The people in London should certainly have included Schild, who had introduced the idea of dose-ratios and the pA scale for measuring the affinity - or dissociation - constants of antagonists. Incidentally his automated equipment, based on post-office telephone relays, must have given Stephenson ideas for the machines he made for his own work. Another world player who should be mentioned is Furchgott. I think he was roughly the same age as Stephenson and they thought along similar lines. It was recognised that you could measure the affinity of an

antagonist or a partial agonist but although you could use an irreversible blocking agent to flatten the dose-response curve of a full agonist and so calculate an affinity constant, this had to be "apparent" because it was doubtful whether it was really an equilibrium constant.

Many people found the idea of efficacy, or intrinsic activity, difficult to grasp. You can picture a drug binding but it's not easy to picture how compounds can differ in their ability go from binding to response. It is possible that their thinking was influenced by things such as the all-or-none nature of transmission at the neuromuscular junction. Clark had even suggested that the action of a drug at a receptor was also all-or-none. Nowadays, though with the involvement of second messengers, it may be easier to accept that different drugs can produce different amounts of these but it's still a problem when the receptor is linked to an ion channel.

In the work with Stephenson and Ken Scott, we were looking at the effects of increasing the size on the quaternary ammonium group in acetylcholine. Ing had showed that as you replace methyl groups by ethyl ones, activity at the muscarinic receptors in guinea-pig ileum declined. Is this because the compounds aren't so good at fitting the receptors or because they don't activate them so well? If you replace hydrogen by something larger such as phenyl in the acetyl group at the other end of the molecule, you obtain a competitive antagonist and so you can measure its affinity. When you replace methyl groups on the quaternary nitrogen by ethyl groups the affinity increases, until you replace the last methyl group. This occurred with five series of antagonists with 4 compounds in each series. If you get the same effect of affinity in the agonists, the decline in activity must be due to a decline in efficacy.

Unfortunately we later extended the series to include pyrrolidine and piperidine rings and found different effects in different series, so we weren't justified in assuming that the changes in the affinity of the antagonists would tell us about the changes in the affinity of the agonists. Which brings me to a world player in a scene not unrelated to receptor theory, Corwin Hansch.

The relations between chemical structure and biological activity have been of interest ever since it first became possible to measure biological activity. In some situations, such as the Overton and Meyer theory of anaethetics, these can be made quantitively and Corwin Hansch and his colleagues derived an equation relating biological activity to chemical properties which was supposed to be of general application. Activity was expressed as the logarithm of the reciprocal of the effective concentration (log1/C) and related to two measures (pi and sigma) of chemical properties in an equation containing 4 terms. From a pilot group of results it was possible to fit values of log1/C, to values of pi and sigma by least-squares and calculate the coefficients of the 4 terms. These could then be used, in theory, to predict the value of log1/C for a new compound whose pi and sigma values were known. The fitting required a computer and if the idea worked it promised to save immense amounts of money by avoiding the making and testing of inactive compounds.

The affinity of a competitive antagonist is as fundamental a measure of biological activity as you can hope for. During my time at Edinburgh we measured the affinity constants of over 200 hundred compounds and I came to the conclusion that it wasn't possible to predict the affinity of new compounds. This is because what you measure, an equilibrium constant, depends on the free energy of adsorption but this is determined by two factors, the change in enthalpy and the change in entropy. So Hansch was trying to use one equation to solve two unknowns. The compounds were useful, however, because they could be used to try to differentiate between muscarinic receptors in different tissues.

Why was Edinburgh such as key place in the receptor story?
Because Gaddum had followed Clark there. Because it was a good place to work. Edinburgh is an attractive city. Because there was enough money - the work wasn't expensive. Because the Central Medical Library was just downstairs - Clark was very active in setting it up. Perhaps the time is as important as the place. There seemed to be less need to justify everything you did and could get on with the work.

Were there any links with James Black?
No. James Black was at Glasgow when I was there but he worked at the Vet. College and I worked in Chemistry and our paths didn't cross.

Well, the reason to raise James Black's name is to ask a broader question - when did the capcaity of the industry to make drugs that targeted a particular receptor to produce clinical diferences begin to come into the story? Because up until this, what you guys had been doing, it would appear to me, was relatively pure science - not linked with what happens clinically too much. But there is a point then when the industry began to realize "There are all these receptors, why don't we make drugs to target particular receptors?" Black was a key person in this it seems.
I don't think it's true to say that academic research was not directed towards producing things. Raymond Ing had a practical use in mind – he wanted to produce substitutes for atropine during the war, neuromuscular blocking agents. The difference was that in academic research at that time you had a chance to try to find out how things worked even if this brought no obvious marketable product. Identifying receptors depends on having antagonists and one of the problems is to get the chemists who make them to understand the pharmacologists as well as the other way round. In actual fact most academic pharmacology departments existed to teach medical students and their research was concerned with drugs already in use. Very few had a chemical input.

On the industrial side I think there have been profound changes in drug testing. When I started the industrial approach was pragmatic, people were quite happy to measure inhibition as a percentage reduction in the effect of an agonist. The more you know, the better tests you can design so the more you can trust the results. This was something that Black brought to industrial pharmacology, along with his medical background. You need someone who can see the medical needs but who can also think about what is going on. I think this combination is unusual.

I'm intrigued to hear you say that very few pharmacology department actually had a chemistry input to them.
I think the situation at Oxford was unique - and ideal. When I was in the department Burn was a live wire - he's one of my heroes. He had gathered a remarkable team around him which included Hugh Blaschko in biochemical pharmacology and Edith Bulbring, as well as Ing, an extremely competent head technician, Ling, and the junior staff which included at various times Geoffrey Dawes, Ellis Baker, John Walker, Miles Vaughan Williams - all with medical backgrounds. There was a lab for 2 chemists in the basement - I was its first inhabitant. The Dyson-Perrins organic chemistry lab was next door and the Radcliffe Science Library just along the road. In these conditions things ought to work. There were chemistry departments in schools of pharmacy, but the pharmacology departments were concerned mostly with teaching, with the exception of The School of Pharmacy at Brunswick Square in London, where Burn had been the first professor of Pharmacology. The School of Pharmacy at Chelsea was also active and there was a productive chemistry section headed by Peter Hey in the department at Leeds. But few medical schools had a chemist. There was none at Cambridge until Arnold Burgen's appointment in the 60s. Dundee was unusual in having a chemist - and like Edinburgh it had a course in pharmacology as a science subject.

I think nowadays things have gone backwards, and this started with the recession in the early 1970s, which reduced the number of chemistry students and their chances of employment. Real progress depends on collaboration - spotting something unusual and knowing where to find someone who can help. You can't afford this, however, when you are short of money and competing with others for students. If you want to build bridges you need a sound footing on each bank. With the present drive for cost-efficiency and the need to plan and account for every detail you find only what you are looking for and it's been my experience that it's the unexpected which produced the big advances. So names get longer (trying to define precisely what you are doing) and management becomes increasingly important but I'm not sure the actual work benefits. I once heard a candidate for a chair say at interview "I'm not a gentleman scientist" as if this was in his favour, asserting his ability to fight his own battles: I felt glad I wasn't working in his department. It made me appreciate how fortunate I have been in the professors I've worked under.

There has been, of course, a big increase in courses in Medicinal Chemistry, which might look like another name for chemical pharmacology, but these are mostly run by Chemistry departments and some chemists' views of biological testing are very different from those actually doing the work.

Someone who has the same kind of background as you was Jeff Watkins.
Yes, and after Edinburgh when I moved to Bristol I had Jeff just along the corridor from me. His main chemistry lab was next door to mine, which was very convenient. He's one of the people who has managed to make it all work. I have known several chemists who have gone the whole way and become pharmacologists - I don't know of anyone who has gone in the reverse direction. Jeff retained his chemical identity at the same time as succeeding in pharmacology.

Jeff seems very similar to you in many ways. He played around with the shape of the drugs and began to say, look! there have to be specific receptors on which these things are working
Yes, I'm sure it is. The principles are the same but he was dealing with amino acids - and again he had Dick Evans. Jeff's success depended very much on good pharmacology - you've got to have both, the pharmacology with the chemistry - and every credit must go to Dick for this.

When did radio-labelling begin to play a part?
In the 1970s. It's difficult to believe that you can take piece of tissue, such as brain, mash it up and get material from it which retains the characteristics of a receptor - that you haven't ruined the thing in the process. A lot of people were sceptical about it. Paton and Rang did some work on the uptake of tritium labelled atropine by smooth muscle in 1965 but the commercial production of suitable labelled ligands only started later. I have a note of a paper in 1971 on the binding of labelled acetylcholine to a phospho-lipid which was not a receptor but by 1975, when I moved to Bristol, radio-ligand binding was well established. I had hands-on experience of it at Mill Hill with Nigel Birdsall and Ed Hulme when we tried to look at the effects of temperature on the binding of muscarinic antagonists to receptor material from rat brain to try to work out enthalpies of binding and compare them with the results of changes in temperature with dose-ratio experiment in tissues. The prodecure was highly organized though in those days you had to cut the bottom off the Eppendorf tubes with a hot scalpel to get the pellet out.

But do you think radio-labelling finally began to persuade people about the existence of receptors?
I think most people already accepted the idea but radio-labelling probably helped the others. It was important because it brought a huge influx of biochemists into pharmacology and physiology lost its dominance. Unfortunately biochemists had their own ways of doing things and had to learn that these are not always appropriate in pharmacology: this applies particularly to some computer methods of analysis of the results.

Why did radio-labelling lead to biochemistry in particular?
Because it's their kind of work. It's not physiology. Biochemistry is a popular subject and there were plenty of biochemistry graduates around.

So the period from the 1950s through to radio-labelling was the classic period really, when the field matured. Radio-labelling since then introduces a whole new era, where receptor number multiplies.
You are asking about the central nervous system, but my contact with drugs in the central nervous system is very limited. I am certainly amazed at the vast range of sub-types of receptor which has appeared since 1990. I think this comes from genetic engineering, rather than simply radio-labelling. In some instances this kind of work has led to the existence of subtypes whose function has yet to be discovered. Things have come a long way from M & D receptors!

Yes. You feel it has to come together in some other way. There has to be something else to pull things together. The receptor did this at one point.

Yes it did, but I think what probably matters is having a selective antagonist for the receptor.

What about the lock and key and magic bullet ideas? These link up notions of therapeutic specificity. In their crudest form in psychiatry you had people saying there are 4 transmitters in the brain - acetylcholine which is the dementia transmitter, dopamine which is the schizophrenia transmitter, 5HT which is the anxiety transmitter and noradrenaline which is the mood transmitter. It became that crude and the receptors in these systems became the targets for the supposed magic bullets that the pharmaceutical industry would produce which would sort out psychiatric illnesses. It became very sloganised. But these very simple points were rallying points for people. Biological psychiatrists thought they could understand the thinking behind all this. But to people like you, how unhelpful were the ways that these ideas about receptors got translated into the wider culture?

In his book "The Mode of Action of Drugs on Cells", Clark had said "...if a pharmacological reaction appears simpler than an analogous reaction in non-living systems, the simplicity must be apparent rather than real". When you come to a subject new, as every generation of students does, you want everything as simple as you can get it. It helps a great deal if you don't have to make exceptions. It's unfortunate that because something's memorable it isn't necessarily right. But you have to learn to live with this. I have no clinical experience so I can't really answer your question. The magic bullet idea was Ehrlich's, just hitting the target and not anything else but this supposes you already understand what is going on. After the discovery in 1940 that sulphonamides acted by inhibiting p-aminobenzoic acid there were pleas for a rational development of chemotherapy but subsequent developments have come from random screening for antiobiotics, rather than from work on the biochemistry of micro-organisms, because you need the blocking agents (the antibiotics) to work out the biochemistry.

Yes and once you show the receptor actually exists, you're powerfully reinforcing that kind of idea, which may not be a hugely helpful idea to reinforce too much.

When you have a receptor you want to make something that is going to affect it and nothing else. This is a chemical problem and if another receptor isn't very different, it's not going to be easy. Some chemists seem to be better than others at coming up with the answers but I doubt if you can design a computer program for it which is going to work. I've already mentioned this. People who work in this field are frequently happy with correlation coefficients which suggest that there is only 1 chance in 10 that the results are random but it is often the compounds which don't fit which are the new discoveries. NIgel Birdsall used to show a slide of the binding of a lot of compounds to muscarinic receptors from two different sources. The values were the same for all the compounds except one, so the chances that the receptors were different are very slight indeed. But the compound which didn't fit the correlation was pirenzepine - which really does differentiate between the muscarinic receptors subtypes. It's like Bill Paton and decamethonium - it's the things you aren't looking for that often lead to major advances.

When did computers start to come into this?
In about 1969 I had to fill in a form stating my anticipated future computing requirements and I wrote "None". Soon afterwards I became interested in estimating size in solution and Barry Lowe in Chemistry showed me how you could obtain apparent molal volumes from measurements of the densities of solutions. A machine had recently come on the market – the Anton Paar density meter - which the department bought and a chemistry student of Dr. Lowe's started making measurements in the pharmacology department with compounds which we had made. He worked out his results using a computer program at the computing centre.

At Barry Lowe's suggestion I went on a 2-week computing course - "You'll enjoy that" he said. So I learnt to punch cards and write simple programs in FORTRAN. Our new professor, Eric Horton, worked on prostaglandins and had a new gas-chromatograph coupled to a mass-spectrometer with a PDP 8 computer, which was supposed to be linked to it. This had 12K of memory and costing £16,000 but the link hadn't been made and it was standing idle. So I had unrestricted use of it and when Doug Waud's papers on fitting dose-response curves to the logistic equation appeared in 1971, I was able to get his methods to work on this machine. These made it possible to fit values of response to dose concentrations by least-squares without the need to transform them into a straight line - such as the Lineweaver-Burk or Scatchard plots used by biochemists.

When the first microcomputers appeared about 5 years later you could do all this at a fraction of the cost and data-handling became completely revolutionised and for most purposes became independent of computer centers. With a Commodore PET I could make the kind of analysis which Corwin Hansch had been doing, that I mentioned above, as well as all sorts of statistical tests. They could also be made to run experiments so you no longer had to design your own automated equipment as Schild and Stephenson did.

Can I take you back through a few figures? You've mentioned Heinz Schild.
Schild was another European refugee and finished up at University College, London. He did a lot of work on histamine and the need to measure the activity of antihistamines seems to have led him to dose-ratios as a means of measuring antagonist activity as expressing it on a pA (logarithmic) scale. Clark was very close to the idea and Gaddum had worked out the effect of competitive antagonists on agonist-receptor occupancy but Schild formalised the idea of measuring the effect by how much you had to increase the agonist to restore the response to its original size. The equation - dose-ratio = 1 + [B]/Kd, where [B] is the concentration of antagonist and Kd is its dissociation constant, is referred to as the Gaddum-Schild equation.

But even arguably pharmacologists don't run with it as much as they should do.
No. If you come to pharmacology through biochemistry you don't see the need for it. All your dose-response curves are hyperbolae and you think in terms of the concentration of antagonist producing 50% inhibition. When you do experiments in pharmacology, and students now do less practical work because it is expensive, you find that dose- response curves vary in steepness. They are logistic, not hyperbolae,

so 50% reduction means different things on different curves. It's tiresome, but there it is.

Who was Cushny?
He was Clark's predecessor at Edinburgh. He had studied in the USA with J J Abel, the founder of the Journal of Pharmacology and he was at University College, London, where he did his work on atropine and its enantiomers before he moved to Edinburgh. He succeeded Sir Thomas Fraser, who had worked with Crum Brown in the Chemistry Department in Edinburgh on the curare-like properties of quaternary ammonium salts. Fraser, Cushny, Clark and Gaddum all had an interest in drug antagonism which can be seen in examples of their work published in 1968 to celebrate "200 Years of Materia Medica at Edinburgh" by the University of Edinburgh. I find it very depressing that 30 years later the Department of Pharmacology has been abolished as part of reorganization.

Finally you've mentioned that J H Burn was one of your heroes. Can you tell me anything more about him? From a psychopharmacology point of view, he's interesting because there are some indicators that he was the first to recognise a re-uptake mechanism - for which Julius Axelrod later got a Nobel Prize. But this was just at the end of his career which may say something about when you should make your discoveries.
In his 1952 book "Practical Pharmacology", Burn explained the potentiation you got with substances like cocaine as being due to inhibition of amine oxidase. In his later years he was very strong on the idea that there was a cholinergic link involved in the release of catecholamines. This was known to apply to the release of adrenaline and noradrenaline from the adrenal medulla but people were sceptical about it's being true elsewhere. Burn's obituary notice, however, contains a reference to work done in 1932 in which he discusses the uptake and release of adrenaline at sympathetic nerve-endings which seems partly to support what you're suggesting, though it's odd this didn't surface at the time of the work on bretylium at the end of the 1950s.

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The classic papers of Barlow, Bulbring, Burn, Gaddum, Patton, Schild, Stephenson and Vane with retrospective commentaries by the authors or others on the conditions leading up to the experiments/papers and the impact of the paper, can be found in:

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