RECEPTORS & CLASSICAL PHARMACOLOGY
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Where did the receptor story start?

Well for my money the story starts with Langley. I remember giving a review paper at some conference and in the process of typing out my contribution, I mentioned Langley (1878) and the typist in the office wrote 1978. This was 1978 and the penny dropped that that conference, therefore, was a 100 years after the first mention of the receptor idea. He didn't use the term receptor but he was very precise. He was discussing the actions of pilocarpine and atropine and he said quite clearly, if one thing is combining with something in the cell and the other thing is combining to prevent the action of the first one, then there essentially must be competition at a site. He didn't use the word compete but he more or less invoked the law of mass action.

He started talking about a receptive substance in 1905. Whether it was Clark then later or whether it had happened in between, the term receptors came into use. I don't know what people thought drugs did before that. Just somehow things happened. I suppose it was only people with a certain kind of thought process who thought there had to be this kind of mechanism. Clark came up with these wonderful notions that the shape of the dose response curve was due to the law of mass action with acetylcholine acting on receptors in the frog heart and the frog rectus. He experimented and produced these curves which more or less fitted but it was all I think very dodgy. For instance, in the frog heart you do in fact get a fairly steep log dose response relationship. But he did the experiments over a long period of time and pooled all the results from hearts with different sensitivities. When he pooled all his results, he got a much flatter curve than the steep one that individual frog hearts would give you and this is what led to his theories. He obviously hadn't had much of a scientific training but he had a very enquiring mind. There is no doubt he really started this field of thought and discussion in terms of receptors. Then Gaddum contributed the crucial step, which was defining the equations expected for competition, again between acetylcholine and atropine. If you look at Clark's results from way back with acetylcholine and atropine, lo and behold, they fit Gaddum's equations marvellously.

Can we try and pick up your input to all this from the start? You trained in Oxford with Burn, was that right?

I originally did chemistry in Birmingham and I was sent to Oxford to do some tests on some compounds that were made in Birmingham during the last War. Somebody had the idea in the Birmingham Chemistry Department, that the whole of chemistry was based on coal tar and obviously this was a limited resource and one day coal would run out. What would the chemical industry do then? We need a renewable resource. Cane sugar was their answer. The chemistry department was directed by W N Howarth. He had various people working with him and between them they resolved the structure of sugar. The hexoses have a backbone of 6 carbon atoms in a ring structure. Cane sugar is two hexoses joined together. So this gave a starting point for synthetic chemistry of carbon compounds and they got grants from the Colonial Products Research Corporation to explore this. One of the things they were exploring was the possibility of making compounds with aspirin like actions. Some postgraduates in the research group produced a dozen or so of these compounds.

Howarth then wrote to J H Burn in Oxford and asked if he could test these to see if they

had an aspirin-like action. This was research going on during the War, 1943 o4 1944. Burn said, he didn't have anybody who could do this but Howarth said, we have some people about to graduate and that the Council would approve finance for one of them to work in Oxford. So I became a pharmacologist. I was sent to Burns' Department in Oxford and spent a year sticking thermometers up rat's backsides, having injected yeast subcutaneously the day before to give them a fever. I knew nothing about this - I was doing what I was told to do. This produced an elevated temperature. The following day I measured the temperatures, I injected these substances and then followed the temperature, comparing the effects with aspirin. Some of them worked and I was merrily going on doing this for 12 months. At the end of 12 months, Burns thought I ought to have a more general education in pharmacology so he got Howarth to send somebody else along to continue doing these antipyretic tests and John Vane became a pharmacologist. His interest in aspirin-like compounds proved rather more persistent than mine!

Your more broad training involved what?
Burn had been sent some compounds by an Indian chemist. These were derivatives of connessine. There were 3 compounds and they hadn't been generally tested, although they had had some use in India. Burn put me on to doing a pharmacological run through of these things, as a means of training me in the procedures. They weren't particularly interesting. At that time, Burn had an interest in quinidine and its effect on the heart - there wasn't much known about how any of these things worked on the heart, or anything else for that matter. There were one or two people in the Department working on quinidine and I remember I put connessine through all the procedures, they were putting quinidine through. I was even sent off to London to work with Goodwin for a week to test whether these alkaloids had any anti-malarial activity. There is a paper somewhere with my name on it.

Can you tell me anything else about Burn because he was obviously a big name? Indeed he was. He had Ing, the chemist, working in his department and Blaschko, the biochemist. This was an indication of his stature and the way he was organising things. He made his own reputation on biological standardisation. He introduced methods for standardising the effects of digitalis among many others. If you inject digitalis intravenously in pigeons, they start vomiting or trying to vomit and he built an assay based on this. He was often asked how he knew when pigeons were being sick to which he said, "well actually it just looks likes a pigeon being sick" - which it did. He used to demonstrate to medical students – there was quite a bit on biological standardisation on their course, this being his thing. One day, one of the pigeons got loose in the lecture theatre. It was a lecture theatre which iron bars bracing on the roof. This pigeon was flying about and we were throwing chalk and all sorts of things at it to try and get it to come down again. It had been living in a cage for months, so it wasn't very energetic and after we disturbed it a few times, it perched on an angle of these ironworks and just refused to budge. I was rather agile and there was one of these ropes used to roll up screens so I climbed this rope, thinking I would disturb the pigeon. I got hold of it and I remember I had to slide down the rope with the pigeon in one hand, hanging on to the rope with the other. Not very pharmacological, is it?

Burn made his name at the Pharmaceutical Society and was appointed to the Chair in Oxford. When I arrived in the Department, he had just come back from the first tour

anybody had made post War. The European War had just finished and Burn had been to the States for a fortnight. This was quite amazing. Whitteridge, who was working in the Department of Physiology coined the phrase that the Department of Pharmacology fiddled while Burn roamed.

How long did you stay there?
I was 18 months there and then I went to Bristol. I was 18 months in Bristol as a research assistant to Dr Heller, a senior lecturer in physiology in Bristol, who formed a separate department of pharmacology. At that time there were very few Departments of Pharmacology about. Manchester had a separate Department. Bristol, I suppose was going the same way as all the others. Heller had a separate department but he was only a Reader and spent a fair bit of his time agitating to get a Chair, which he eventually did. I wasn't at all impressed with him as a scientist but I did assist in his kidney research on rats - sodium and potassium measurements.

I remember we seemed to be getting higher sodium, than we thought was right. So he thought we probably weren't cleaning the glassware properly. We collected the urine in 10 ml measuring cylinders. After these were used, they went into chromic acid and rinsed under the tap and they were rinsed very thoroughly and then filled with distilled water and left overnight. The distilled water was then emptied out. Heller thought this wasn't good enough. There must be some sodium contamination left because we were getting these high figures. So he turned up with a special handkerchief that his wife had given him, we were to clean the insides of the cylinders with these after the cleaning process. I worked out that the extra sodium we were getting, was equivalent to about a gram of sodium chloride and it didn't seem that we could really be missing a gram of sodium chloride.

I was there for a year and I fiddled around with a few things. The thing I got really interested in was what histamine acts on. Histamine exists as a base and there are 2 dissociations, although only one is relevant at physiological levels. But is it the cation or the free base that acts? I suppose I was triggered to think this because I came across a paper by Trevan and Hook, who had played with changing the pH of local anaesthetic solutions on the rabbit corneal test and concluded that it was the free base of the local anaesthetics that produced the activity rather than the ion. I thought well if this could be shown in this way, could I work out in the case of histamine whether it was the base or the cation, which was active? Since acetylcholine and histamine both make the guinea pig gut contract, and acetylcholine doesn't change with pH, all I would have to do is just run assays comparing acetylcholine and histamine at different pHs. I did this and there was no difference. It didn't matter what the pH was, the ratio between histamine and acetylcholine was the same. So I started thinking well if the histamine is combining with the receptor and whichever species is combining must change, concentration, with pH, then maybe the receptor is dissociating in a way that matches or compensates for this, so that it may just be coincidence that these things balance out. I thought that if I could get hold of some anti-histamines that had different dissociation constants they would dissociate over a different pH range, then by comparing how the antagonists change with pH, I might get somewhere. But around this time, Gaddum offered me the job in Edinburgh, so I of course accepted that.

The anti-histamines, had they begun to come out then?

They were just arriving. Bovet began it but all the companies were on the bandwagon by this time.

It's hard now to see the anti-histamines as being awfully exciting, why did they seem so exciting then?
Because they were synthethic and they were a new class of drug with a very specific action. There weren't all that many synthetic drugs around. These had been created with a specific object in mind. I think Bovet had originally being looking for an anti-adrenal action and found something which was more effective against histamine. Later it became even more interesting when it became clear that the anti-histamines would block reactions to histamine except gastric secretion. This was a puzzle, which nobody really, until Black not all that long ago, realised that this meant that there were 2 different receptors. I don't think the penny dropped with me actually but once the idea came out it was obvious. Soon after that there was the alpha and beta separation of the adrenal receptor proposed by Ahlquist.

Ahlquist was a funny chap. First he tried to get that paper published by the American Journal of Pharmacology who refused to print it. So it appeared in the Journal of Physiology. I saw him at a conference somewhere, where this subject came up. He believed in doing all his experiments in whole animals. During this lecture, he poured scorn on people who worked on isolated tissues. You had to look at the whole animal and his work was measuring blood pressure and other things but all in the whole animal. He told the story in his lecture about the 3 blind men feeling the elephant and one got hold of a leg and said it was a tree. The other gets hold of the tail and says it's a rope and the other gets hold of the trunk and says something else. I got up afterwards and asked him which sixth sense he used to look at the whole animal because I felt he was clearly implying that there was a sixth sense involved. He didn't realise that what he was implying. I think a few people in the audience appreciated what I was asking. I found him distinctly unimpressive there but the alpha beta distinction was a major, major step.

Okay, the anti-histamines had just begun to come on stream and then you were offered a post in Edinburgh.
I'd enrolled to do a PhD in Bristol on this histamine idea. I'd built up a bit of a collection of anti-histamines with different pKa values - I got the manufacturers to tell me what the pKa's were. I don't know whether I had done the odd experiment but I could see this being very complicated. Comparing acetylcholine and histamine over several different times and different pHs – well the guts weren't very happy. You could run them quite happily at one pH and you could change to another pH – I was using borate buffers - but then if you changed back it didn't work so well. I thought this was going to get too complicated to embark on as a PhD subject in Edinburgh, so I looked around for something else to do.

Anyway before this I had read Clark's papers and thought how marvellous – something so simple as the mass law determining the shape of the dose-response curve. Almost too good to be true and of course it wasn't true.

Was Clark's ghost around the Edinburgh Department.
It was in the mind of Condon, the chief technician. He was a great admirer of Clark and

had rather fallen out with Gaddum. Condon had done a lot of the experimental work and if somebody was working on an animal, Condon set the animal up also for the teaching, and the lectures. Gaddum said he couldn't do this, he didn't have a license and so Condon was relegated to the workshop, where he was reasonably handy but he resented having been removed from the centre of things.

You heard all sorts of great tales about Clark. How marvellous he was. That if an isolated frog heart wasn't working properly, he would taste the Locke solution and then perhaps say that a bit more potassium was needed and so on. I remember a time when Condon told us how great an experimentalist Clark was - he could make anything work. He used to tie frogs' hearts onto the cannula with silk from his tie. He used to pull a thread of silk out of his tie and tie the frog heart onto the cannula with this. Of course if you are pulling on this, sometimes one end breaks. Anyway one day it broke and the heart flew off. Apparently Clark fished the heart back out from under the pipes at the back of the bench, where it had gone, scraping it out with a ruler and it still worked. So I wasn't too surprised to see that in Clark's records there were different sensitivities in different frog hearts. Of course sensitivity also varies seasonally. Winter frogs were the proper ones to work on, so the frogs used to be kept in fridges, to make them think it was winter.

Gosh. There's an awful lot of lore to all this, isn't there? You'd wonder if pharmacology to some extent has lost all that.
I expect it has. None of the papers then ever referred to the fact that when you were using a smoked drum to record the contractions of a frog rectus which was slow, you tapped a bench all the time to overcome the friction between the writing point and the smoked paper. If you didn't tap it you got jerks on the tracing but this was never written up.

Extraordinary, so really these things might all be unreproducible now.
Well not all entirely unreproducible. You can use different methods. I always had some vibration built into my equipment - usually the stirrer on the organ bath was effective. I think Vane mentions this vibration in the introduction to one of his pieces.

Fascinating. What can you tell me about Gaddum himself?
He was a mathematician originally. I think he did maths in Cambridge before doing the pre-clinical years and before he went off to a London Hospital. I know very little about his background. It's a German sort of name. The only other Gaddum I have ever heard of is currently the Vice something or other of the Bundesbank in Germany.

I am not very good talking about people. Derek Dunlop who was on the Committee for Therapeutics is reputed to have said that Gaddum was vain. I can see what he meant but he didn't appear oppressively so. He had no interest in administration. Would take no part in committees in the university. I suppose he occasionally went to some but generally he kept entirely clear of that. He was a highly intelligent man, there is no doubt about that, which you can't always say of medically qualified people.

What led him to make the contribution to receptor theory that he did – both the mathematical stuff and the M and D receptors.
That's interesting. It goes back to the basis of biological standardisation. There are

different ways to do it. You can have a reproducible response from the tissue and use repeated responses graded in size with the dose, or an all or none response in a group of animals - the frog or the cat assay for digitalis. What you did was you took a group of frogs and gave them a dose that killed some of them. You gave another group different doses that killed more and so on. And you did groups of animals with the test substance. Now, if you took several groups of animals and you measured the percentage mortality, you got a curve. Trevan introduced ED50 as being the right point at which to make the comparison. Now if you looked at the whole curve you find that there is a straight line in the middle and if you take two points above and below the ED50 point you can get a good estimate of potency.

Now the fact that you had just such a curve made some people, Gaddum among them, think that perhaps the dose response curve in an isolated tissue represented separate cells responding. You had population of cells with different sensitivities, so some went off on the low doses and some went on the higher doses. He told me once that he had spent some time with a frog rectus, trying to see if the contraction could be divided into steps. He set up an optical system, with a mirror on a spring, which rotated as the muscle contracted, using magnification across the length of the room. He looked to see if he could see the steps corresponding to his hypothesis but he never found any. Then I think he read the Clark paper on mass action. Being a mathematician, he went on to look at competition in these terms.

He had moved to Edinburgh around 42/43 when Clark had died?
Yes, I didn't realise how recently Clark had died when I moved. I didn't know anything about Clark as a person before I came to Edinburgh. I had certainly read his crucial papers before I came to Edinburgh. I don't know just how seriously I'd thought about them. It was a significant new idea - Langley's contribution had been forgotten - and Gaddum believed in it. He was quite taken aback when I pointed out to him that his own work with adrenaline and the rabbit uterus did not fit this picture. I think Clark must have had great charisma and he had a reputation in other areas.

Gaddum also recruited like people Marthe Vogt. How did that come about?
I don't know. She was there before I came. I think the migration of German pharmacologists, escaping Nazi Germany to Britain was fairly general - Edith Bulbring was in Oxford, Marthe Vogt was in Edinburgh, Hans Kosterlitz went to Aberdeen, although it was much latter before he made a name for himself - Wilhelm Feldberg was in Cambridge and then Mill Hill.

Now 5HT began to come into the story at this point through LSD, out of which came the idea that the 5HT in our brain is what keeps us sane and the 5HT receptors, the M and D receptors.
I remember there was a time when nobody at a conference got up to give anything about 5HT and LSD without referring to Gaddum having started this line of thought. But I was not involved myself with 5HT, nor with substance P, first isolated from urine, hence the name, which was also investigated.

At this stage then what were you actually working on in the lab - acetylcholine?
Yes, acetylcholine and atropine. I can't recall just when I started doing this. I fiddled about doing various things. I remember I built a flame photometer because somebody

showed an interest - I physically built one; they weren't available as purchased equipment. The crucial thing to starting the receptor work was that Gaddum got agreement to appoint a new lecturer. Gaddum asked me if I had any ideas about this. I suggested he get Dick Barlow, who had been working in Glasgow in a Chemistry Department. He had worked with Ing in the Oxford lab at the same time as I was there. Although, he was working in a Chemistry Department, he was writing a book about pharmacology. Gaddum offered him the job and he came. I wouldn't have been able to do it if it hadn't have been for Dick and his compounds. But after doing the work, my recollection is that it took me longer to write the paper than it did to do the work. I spent about 3 years writing the paper and never submitted a thesis for PhD.

Can you put in terms that will make sense to the average neuroscientist, what the importance of the different view of receptors that this paper produced was?
I don't know that it did change how we view receptors really. It made the interpretation of some experimental research more sensible. The idea up to that time following Clark was that the shape of the dose response curve was determined by the mass law action relating the interaction of an agonist with a receptor. I established that that is clearly not true. I introduced the idea of spare receptors - that is you can get the maximum response from quite a small proportion of the receptors in experiments with isolated tissues.

I also suggested that the interaction of an agonist and a receptor might not be necessarily all or none. Different agonists might invoke greater or lesser responses at the receptor. Now I don't know whether this is true or not but it fitted the experimental results well. It may be true in some situations and not in others. But I think the clear recognition that there isn't a linear one to one relationship between receptor occupancy and the ultimate response is so much more realistic than the previous view.

What does this do for our image of receptors in lock and key terms. It makes the whole thing a lot more fluid in a sense.
Yes, well I always used to think of it in terms of what the agonist does to the molecule to which it attaches itself. It induces some conformational change in the receptor molecule. Part of the molecule of the receptor must change, so that further down the line something else starts happening that didn't previously happen. Now it seems reasonable in those terms that a different agonist will not produce as much conformational change as another so that whatever happens further along the line, perhaps doesn't happen as quickly. In the case of acetylcholine, one assumes that acetylcholine produces the optimum change in configuration and other things don't produce as much with a consequent less effect. But that's my speculation.

Incidentally while we are at it, I must rehearse my favourite prejudice. The term receptor has now come to include the whole of the things, which have been isolated – the whole protein that goes all the way through the cell membrane and comes out on the other side. For my money, the receptor is that bit, whatever it is, the drug molecule combines with. All the rest is the rest. It's not the receptor. Since they started isolating receptors, the thing they isolate has become what people think of as the receptor. I assume in many cases it's a channel that's involved and the agonist is causing a channel to open. So in the case of the conformational change I was talking about, a less than optimal action probably doesn't open the channel quite as wide, so

not quite as much stuff gets through.

The competitors at the time were the Dutch - Ariens and people like this who had a completely different view to yours.
Well Ariens started of course with the action of sulphonamides on bacteria, where they block something or other. He saw there was a competition between this whatever it is and the sulphonamide and the bacteria couldn't grow without the substrates. He found there were differences between different sulphonamides when it came to competition and he moved from there to drug interactions, where he got similar results to mine. But he didn't accept immediately this business that you didn't need all the receptors to produce a response. He had a different view on the intrinsic activity that a drug had. Acetylcholine in our case had an intrinsic activity of one and will produce a maximum contraction. But other substances won't produce a maximum contraction. If they produce half the maximum, they have an intrinsic activity of a half. My postulate was that drugs which had a lower efficacy than acetylcholine can still produce a maximum contraction. Ariens didn't recognise this.

His was a very enzyme based view isn't it?
I think it came from enzyme kinetics.

Then there was Bill Paton's rate theory.
It had its interest. When he got up at the Pharm Soc and read his paper on it, I got up and argued against it there and then. We had quite an argument. I gave a paper at a later meeting, in which I criticised this view and he got up and criticised me – but we were on very good terms. But, I never took the theory seriously. There might be circumstances where it is applicable.

At that stage we used to have Honours students take copies of papers like this and criticise them. There were 7 or 8 students and I remember we set questions for the honours exam on these issues. One year we had a question about rate theory and one chap, more or less started off his answer by saying "judging by the way Stephenson and Ginsborg laugh about it, it can't be taken very seriously". This was in a paper for which Paton was the external examiner. I don't recall any comment being made in the Examiners Meeting.

Furchgott was one of the few other people who plays a role in this.
Yes, he was an American. He was interested in this field and he wrote papers, some of which made sense. We were both invited to a meeting where he circulated a paper beforehand about measuring affinity constants for agonists by following them through as you used an irreversible antagonist. I had worked out a method for getting the affinity constants of partial and full agonists and I read a paper about it at that meeting before he was due to give the paper, which he had circulated before. He withdrew that one and he was up half the night producing a new paper the next day which was full of the most incredible equations which nobody could follow. After the conference there was an opportunity to write our papers up for some Journal. I said I wasn't going to write it up then and I never did write it up properly but he went away and he wrote it up. So some of what I had said appeared in print under his name.

At any of these meetings, did you have to still talk about "putative receptors"?

Was there still a feeling that maybe these things didn't really exist. They hadn't been labelled. They hadn't been isolated. They were hypothetical entities in some sense.
I remember once being invited to address students in Oslo. Beforehand I was asked to give a title and I said off the top of my head, "why do we believe in receptors" or something like that. When I got there, I got up and I said that the main reason why we believe in receptors is because nobody has thought of a better idea and I can sit down now. Of course, I didn't sit down, but that sums up my view about it. I think people just didn't think about it. Drugs did what drugs did. You could work out the physiology of what they did - how they interfered in physiological situations. But what the immediate prime thing they acted on was, I don't think anybody cared about that.

I remember after one lecture to the British Pharmacological Society, where I discussed some of the ideas, some chap got up and was very disparaging. He said this was much the same as the medieval dissertations about how many angels could dance on the head of a pin. I don't know how widespread that view or attitude was. I don't know what he thought drugs did. It perhaps comes down to the question of when did vitalism die? The idea that there was something magical about living processes and it has got nothing to do with mechanics. I think that idea had not entirely really died.

Howarth was the first man to synthesise a vitamin - Vitamin C. He synthesised it and made a big name for himself. That, one always was told, was one of the biggest nails in the coffin of vitalism. That functioning was a matter of chemistry. But I don't think the idea was dead among medical people. It might have been dead notionally – that is they took the position that whether it was chemistry or not, it was so complicated that it was unknowable anyway, so why worry, just get on with it.

The ghost could still hover in the machinery. Does the receptor story interact much the disputes between the physiologists about the fact that neurotransmission is electrical versus chemical. The chemical view is a very particulate and mechanical view – chemicals and receptors. The electrical view is more vitalistic in some sense.
I hadn't thought of it in quite these terms, but yes I think this idea was there. It was only a year or two before my time that the chemical theory was really established. As far as I was concerned, the chemical theory was established, but there were still people around who didn't accept it. You certainly still heard talk about putative neurotransmitters.

Acetylcholine for a long time was the only neurotransmitter, where it was accepted that it met all that criteria for a neurotransmitter. The others were putative neurotransmitters weren't they?
Well I don't know. I mean there was some extraordinary theory about adrenaline in the textbooks when I first started. Cannon and Rossenblueth, a couple of Americans had this theory, that nerves released sympathin which interacted with the muscle or heart and the tissue decided whether contraction or relaxation was produced. This was before noradrenaline had been synthesised and tested. The nerve was the same while the thing it interacted with was supposedly different. It didn't make sense to me when I read it.

When they began to radio-label receptors, that in a sense changed the whole debate because clearly something did exist. When did you become aware of radio-labelling first? In one sense it proved receptors were there but from your point of view radio-labelling must have also looked like a step backwards in the sense that they took a very enzyme approach towards the receptor.
I had nothing against the enzyme approach. I think there was that sort of feeling about it. I remember radio-active potassium and a lot of these studies with nerve tissue as being one the stages of my being aware of that sort of thing coming in to light. There were times when I wondered whether I ought to be getting more involved but I decided it was not for me.

We have talked about the receptor in terms of its being a mechanical thing. But it's also the thing that underpins notions of specificity in a way that perhaps can become too reductionist.
I don't think I see that. It seems to me that specificity is what it is all about. Period.

I can see when you are operating in a gut bath or whatever specificity is just what you want. But when you are operating clinically, I wonder whether an exclusive focus on specificity cannot be a drawback on occasions. Once if you start thinking that getting the right drug for the right receptor as opposed to the right interaction between the doctor and patient is what counts, there can be problems. Can you see any of this?
No. I mean. If the drug works, the drug works. What the doctor patient relationship is, is an entirely different matter. It's nothing to do with the pharmacology of whether this drug is highly specific for this receptor and may have a minor or significant effect on another site. If one has a receptor identified as being relevant to some condition you want to treat, then you want a drug which is highly specific for that receptor, whether as an antagonist or as an agonist or maybe even something in between.

I am mildly disappointed in that so far as I am aware nobody has yet developed a partial agonist for clinical use. There are cases where you don't want too much of an agonist action. By overdosing, you get much more than you want to but if there were a partial agonist with the right degree of the activity, you can't get too much activity.

Okay. The way things have played out, specificity, it seems to me has trumped something else, which you referred to, which is the fact that there can be a range of individual sensitivities – as in rats hearts or the frog.
The frog is a special case. I don't know if there is all that much variation between different healthy mammals and in isolated tissues in my experience differences in sensitivity are largely due to the handling the tissue has had. There is no discussion in Clark's papers, as far as I can remember. He just produces a dot diagram of all his results from all his experiments as far as I can guess, covering hearts at different times of the year, whether they had been scrapped out from under the pipes at the back of the laboratory or had some extra potassium thrown in to the Locke solution. I have no doubt that frog tissues vary very markedly and this is partly seasonal. I don't know that mammalian tissues do to anything like the same extent. The uterus varies with the hormonal state of the animal from which it comes and I am sure there are plenty of other similar things but I doubt whether there is all that much intrinsic variation between tissues that are healthy. I suspect most of that variation is induced by external

agencies. Central nervous systems are of such complexity, that there are certainly going to be differences there. But I would have thought that if there was a genetic failure to produce the receptor properly it just wouldn't function at all.

Well receptor variants are a big thing these days. What they claim these days is that the D-2 receptor, when it is exposed to dopamine, turns in and inverts, as it were. Now there are some variants and the claim is that these may lead to less inversion.
I retired 10 years ago and am not familiar with the experimental evidence, but from what you say this seems to confirm what I said. The agonist-receptor interaction induces a conformational change in the adjacent protein and partial agonists produce less change.

I think they are coming to be seen as part of the normal spectrum – the idea that we don't all have the same D2 receptor. There are different variants and different densities.
Well, there was Collier's notion that the receptors are constantly being renewed. .

Another receptor issue links to the disease model. At the moment, we have the idea that the receptor is the locus of a disease - that almost all diseases at some point will be shown to involve a lesion of one receptor or other. You get the idea partly because the drug is act on the receptor and drugs act to cure the disease but is there a potential fault in logic here?
Are you referring to what I would term the receptor or are you including what lies beyond. I mean after all, you can say that every enzyme is a receptor but on the whole, I prefer to leave enzymes to the biochemists. I suppose basically receptors as I see them are the acetylcholine receptor, adrenoreceptors and the HT receptors. Gaba etc etc.

But, do you take my point at all that diseases are probably disorders of systems but we tend to think of the lesion as being based at the receptor level
This is not a subject I have thought about greatly. The receptor starts something off and a whole chain of events happen thereafter. Just on a probability basis, there is so much more to go wrong further down the line. So again it depends on what you are calling a receptor. If you take the receptors as being the whole channel including what wags the tail, inside the cell, then I suppose there's more room for things going wrong there, which some people would say was the receptor failure but I wouldn't.

Is there scope, the way you see the receptor, for drugs to act on things other than the receptor? Could they act on the second messenger system themselves rather than on the receptor.
Well, this becomes semantics. On the whole, I suppose I have always thought of receptors in terms of what the evolutionary process has produced an agonist for. It produced the 2 things together. But clearly you can interfere with molecules at any old site, which wouldn't be a receptor in the traditional sense but is a receptor in the sense of ligand binding. This can be anywhere unlike the receptor.

So in the case of something like what's called the NMDA receptor these days, a huge big complex thing on which different things act on various different points,

but glutamate will act on perhaps the one point, which you would call the receptor, what should we actually be calling the rest of that complex?
I don't know. Find out what's it's there for and that will decide it. It's presumably part of a structure supporting the receptor. The receptor might comprise of an atom or two on one bit of molecule and the thing folds in such a way that something else comes close and that's another point. I tend to see the receptors as 3 point attachment things – not for any good reason – except because of stereospecificity. The 3 points could be on very different parts of a molecule or different molecules. And a lot of the rest of the molecules are there perhaps just to hold these critical points in the right place - to form the receptor. Presumably they have to be such that they are modified by the agonist attaching itself so that whatever happens next, happens.

It seems that a number of people who were interested in receptors came to it from a chemistry rather than a physiological background. How much was receptor thinking driven by the fact that things like stereospecificity almost demand a receptor?
I think it contributed very considerably to the notion. It was very difficult to get away from stereospecificity. And also chemistry is about the interaction of molecules and receptors are all about the interaction of molecules. It was just a natural way for chemists to think.

At what point were did the capacity of industry to produce drugs which targetted different receptors begin to play a part in all this.
Black was the person who made the difference. He was the one person who deliberately set out to produce a drug which would act with receptors. That was a key breakthrough. I never had very much to do with industry, so I am not particularly knowledgeable about all this but my impression certainly was that Black was the first person to seriously look for a particular substance to act on particular receptors to do clinical things as distinct from pharmacologists and chemists who were looking for drugs to do things however they did it.

I was rather surprised, when I had been around for 10 years or so in pharmacology, to realise that it was chemists in drug houses who drove things. It was chemists who decided what compounds could be made. They would just hand them over to pharmacologists to test. It wasn't pharmacologists telling the chemists what to make, as far as I could tell. As I say, I had no great knowledge of pharmaceutical industry but this was my impression, gleaned over the years. The chemists were in charge.

They speculated – if this does that, then if you modify the molecule this way or that way, would that make it better or worse. This sort of thing. Almost like my origins in Birmingham, where people in the Chemistry Department thought their compounds might have an aspirin like action and sent off to Oxford to see if they could test them. I think it was that way in the drug houses. On the whole they are fairly secretive about what they are doing.

If the pharmacologists had been in control, how would things have been different?
I don't know. I suppose I was always mildly irritated with myself that I never thought things through the way Black did with histamine receptors.

Reference

Stephenson RP (1956). A modification of receptor theory. British Journal of Pharmacology 11, 379-393.