THE DISCOVERY OF THE OPIOID PEPTIDES
JOHN HUGHES

Some time back I was interviewing Hannah Steinberg, and she said to me that she felt that one of the key discoveries was the discovery of enkephalin in the brain. This was brought to her in an unusual way when she went to try and get a copy of Nature to photocopy a copy of your article and found that the actual pages for that article had worn away - and this was only about 2 or 3 years after it had come out. Clearly it was a piece of work that caught the imagination not just for people within the field but of the wider public. Can I ask you how it all came about?

Well like many of these things, scientific advances come about because, I guess, the individual scientists get fascinated by a particular problem. Why they get fascinated with that problem is often quite unclear. Okay some of the truly great may be want to understand the origin of life and so you have Watson and Crick and they went straight for it. The rest of us lesser mortals settle for what interests us, perhaps because of baggage we carry from the university, a particular lecture or a supervisor that really turned us on to a particular subject or particular area. Its difficult to say.

I wanted to work in neuroscience. I knew that when then I completed my first degree but I also wanted to do medicine. I tried to combine both. I was at King's College Medical School for a while. But I also registered for a Ph.D under John Vane and spent three very happy years not doing any medicine at all doing research into adrenergic and non-adrenergic, noncholinergic transmission in human and animal blood vessels and at the end of that period I realised how ignorant I was - particularly of the new biochemistry of the brain. It was a period when lots of things were happening particularly in the States.

This was when

This was 66/67. It was the time when adrenergic uptake was being discovered and exploited, the biosynthesis of catecholamines, the serotonin story was beginning, the whole of brain neurochemistry. So I went over to the States, to Yale, to learn some of this new neurochemistry. I guess its your post-doctoral training that sets you in that kind of direction. I therefore became a neurochemist, from having a first degree in biochemistry and pharmacology, a passing acquaintance with medicine and a Ph.D in pharmacology. I was particularly fascinated at that time by what modulates transmission. Every one at that time thought there was only a handfull of neurotransmitters and therefore the key to how the brain functions must be how these transmitters modulate and how they interact with one another. In fact some of my early studies were concerned with quite an important peptide Angiotensin, which facilitates adrenergic transmission in a number of situations. So that was the state of play when I went to Aberdeen.

Why Aberdeen?

Why Aberdeen? I wrote to John Vane, saying I was coming back from Yale, I had certain irons in the fire, one was to do yet another post-doc in London University, at Kings College, perhaps even resume medicine, which was a possibility, another one was to go to Newcastle, where there was a new department of pharmacology being set up. Really I was quite set on the idea of an academic life - it appealed. They were the two I said to John I was thinking about. He wrote back and said well he didn't think there was anything at Newcastle and it would be daft to

do another post-doc but Hans Kosterlitz was setting up a new department in Aberdeen and he thought I ought to go there. He put me in contact with Kosterlitz, who actually visited me in Yale. We got on very well right from the start. Kosterlitz was a fascinating man.

Tell me about him?

Well at that time he was approaching 65 and very unusually the university had waived the normal employment requirements because they wanted to set up pharmacology as an independent entity at Aberdeen. The then Professor of Therapeutics and Materia Medica in whose department Hans was at the time wanted this to happen. They all agreed that Hans should be given a five year extension to his normal tenure. So at the age of 65 he became Professor of Pharmacology in the Department of Materia Medica in the University of Aberdeen.

Remarkable

Absolutely extraordinary. It was a combination of circumstances. This is what the clinical school there wanted. This is what the clinicians wanted. They accepted that eventually it would become a separate department.

Where did he actually come from?

Kosterlitz had been in Aberdeen since 1935 - plus or minus a year or two. He had come over with the rise of Hitler. Although not a Jew himself, he could see what was going on - he had Jewish connections and he was thoroughly disturbed by the whole situation. I don't know if he meant to come over permanently. It may be it was a combination of things. He wanted to work on insulin and intermediary metabolism, he was deeply interested in that, so it just kind of fitted in. I don't know - he's never said that he either intended or didn't intend to go back. As it happened his fiance came and joined him some years later and they got married. They actually ended up in Aberdeen because one of the co- discoverers of insulin, McCleod, was Professor of Physiology there and he wanted to work with this man. Unfortunately this fellow died within a year of Kosterlitz arriving but by that time, you know I guess the way you drift into things, he had decided to stay on at Aberdeen and make a career there. So from Berlin to Aberdeen and he has been there ever since! He was a clinician of course.

You both met and he talked you into coming to Aberdeen.

I didn't need much convincing it was more a question of could I convince him I was a suitable. In those days, although academic jobs were easier to find than they are now, they still weren't that easy to come by. This was obviously a good opportunity. I had never been to Aberdeen in my life. I'd been to Scotland, I'd climbed in Scotland and had a few holidays there but I had never been on the East Coast, apart from Edinburgh. So I really didn't know what it was like. I had no experience of the university. I knew a little bit about Kosterlitz. I had read some of his papers and familiarised myself with his work. But I thought he was a thoroughly nice man and it sounded a good opportunity and who knows if he was going to be retiring in 5 years time, there might be a job there. One perhaps thinks in that way but little did I know, he still hasn't retired, of course. He's 91 now. He doesn't work in the lab but he still goes into the university to his office each day.

He offered the job and I took it. The first time I saw Aberdeen was when I arrived with our cases, on the train, the following September. And the outcome of that was good. In those days I mean it was much freer, much easier - maybe it was Aberdeen, maybe it was Kosterlitz - he gave me a lab, an office, a technician and quite a chunk of apparatus. I told him what apparatus I wanted and he provided it. Plus I was given a small research allowance. So within a month or two, I was on my feet and doing experiments. Within 6 months I had written up an MRC grant and got it. So within a year of getting to Aberdeen I was an independent investigator with my own technician.

Obviously there were quite heavy teaching duties. In comparison with now, I suppose you wouldn't call it heavy but there were thirty medical lectures a year, along with the practicals. We set up a first degree programme in pharmacology within a year as the department expanded from three people to four to five people. But I continued with my research on neuromodulation and that's what Hans was interested in. He was interested in the cholinergic system. Particularly using the guinea pig ileum as a model. I was interested in using blood vessels and the vas deferens as a model. And of course the other interest of Kosterlitz's was opiates.

He had had that for some time, hadn't he?

No - he only got interested after Paton and Schuman published their original paper showing that morphine inhibited acetylcholine release from guinea pig ileum - we are talking mid 60s, early 60s. He had actually applied that knowledge to the adrenergic system - he'd done some experiments with John Thompson, who was funnily enough the Professor of Pharmacology at Newcastle where I had originally wanted to go. He was my Ph.D examiner. He was the reason I wanted to go there; Thompson was a very learned man, a very good experimenter and a very nice man as well. A very very pleasant man - he still is although he's retired now. John Thompson was famous for having developed an isolated preparation of the nictitating membrane of the cat, which is an incredibly tedious preparation which takes anything between an hour and 2 hours to dissect and put in an organ bath. This is a classic medical student experiment - you can do it in vivo; you take the cat and tie the nictitating membrane to a thread and you can show that by stimulating the nerve supply to the membrane you get a contraction that is adrenergic in nature. Well Kosterlitz with Thompson showed that that adrenergic transmission was also morphine sensitive, which was the first time that that had been demonstrated.

When I joined, with my interest in adrenergic transmission, he was on at me right from the start "come on morphine interacts with this you've got to find other models in which this applies" and I'd say "I'm not interested in morphine, morphine's rather boring. Its okay for a medical class demonstration but.." Anyway he kept on and I actually had an interest in drug abuse, drug addiction but I was working from the other side 5HT and LSD and so on.

But it just so happened that there was a young student who wanted to do a PhD with us, from Glasgow, a fellow named Graeme Henderson who is now a Professor of Pharmacology at Bristol. He came to do a PhD with Kosterlitz and myself and we thought about the problem and we said well why don't you look at adrenergic transmission - Kosterlitz hadn't actually measured noradrenaline release, which was my particular forte at the time. So we gave Graeme the task of looking at noradrenaline release from nictitating membrane, which was a very cruel thing to do to a PhD student. It is incredibly difficult preparation - we actually got John Thompson up to Aberdeen to demonstrate it, to show him how to do it but it was still a very complicated, very tricky thing apart from being expensive as well.

Anyway Graeme did a first class job and showed that indeed morphine did inhibit noradrenaline release as you would have predicted from pharmacological experiments but really there was nowhere to go, the nictitating membrane was just too complicated, too expensive. I had been mulling over in my head - you know well lets put him on to see if he can find another adrenergic model that responds to continue his PhD, otherwise we'd have to shift him to something else. He tried a number of preparations without any luck.

It just so happened - I was down at the library one day, I guess this was 70/71, just flicking through the journals and I came across an article in Acta Physiol Scandinavia that showed that the mouse vas deferens was quite a good preparation for looking at noradrenaline release but what caught my attention was that they had done a frequency output curve. Now most people didn't do that at that time. This actually measured how much you got out per pulse, at different nerve frequencies, which is one of the things I had been studying, and to my astonishment the mouse vas deferens appeared to show the same output characteristics as Graeme Henderson had shown for the nictitating membrane which was a morphine sensitive preparation. I wondered if there was a connection there.

So I went back to the lab and said to Graham you know try this - its worth trying and just left him alone. A couple of days later I wandered in and said "did you have any luck with it?" and he said "oh yes I put up the mouse vas deferens and I put morphine in and there it was inhibiting the mouse vas deferens". I said "well that's very good". In fact it wasn't that brilliant - if you got an inhibition it wouldn't wash out and there were a lot of technical problems which we solved over the next few weeks.

That was really the start of my true interest in morphine because there you had an adrenergic transmission which was the love of my life at that time, inhibited by morphine. Now this was fascinating and there was also this frequency relationship which we never explored further in fact because we had already got hold of enough things. Graeme was able to make a PhD thesis out it - in fact we got several PhD theses out of that little preparation.

Then - this is the way the scientist thinks - you get an interest it tickles you, it nags at you and I began asking questions that I guess Kosterlitz had been asking for some time. But it had never occurred to me before - why should there be morphine receptors in the vas deferens, why should they be in the guinea pig ileum for that matter or the nictitating membrane. That was a topic of discussion for a long time between Kosterlitz and myself and others in the group. We knew it was a pharmacological receptor - it had all the characteristics of a classical receptor. And so the idea grew up well that if there is a classical receptor, its not there to interact with morphine perhaps its there to interact with something else.

Now this fitted in with a lot of other stuff that had been going on at that time - work in the States particularly by a fellow called Liebeskind and his PhD student Huda Akic - they had been studying stimulation induced analgesia in rats. They would insert electrodes into the rat's brain, particularly into the periaqueductal grey matter and showed that if you apply the right frequency and current you could get a profound analgesia in the rat. They had taken this a step further than other people - they had localised the action. They showed that the analgesia could at least be partially reversed by naloxone and they reported this observation. They didn't draw any conclusions from it - they were very puzzled by it. I'm not even sure now why they did the experiment - except on the basis that morphine is an analgesic so lets try morphine antagonism.

That seemed to me a very strong hint that there must be something in the brain that actually acts like morphine. And you know this combined with the fact that there was this stereosensitive receptor really fired me up. You know this is too good an opportunity to miss - here we've got all the facts and we've got an assay with which we could test this hypothesis. That was really the starting point.

So something in the brain that attaches to this receptor?

I guess it might not have got any further. I did some preliminary experiments which were negative and we were very busy at that time. We had gotten very much into receptor specificity apart from a general interest in neurochemistry. Hans was fast approaching retirement - this was 1972. It is possible that if Hans had retired I might have carried on for a bit and then given up. About that time, funnily enough, a fellow called Avram Goldstein actually had published a paper, in which he specifically raised the question of whether there could be an endogenous morphine substance in the brain. He reasoned with characteristic straight forward logic that if there was, then you should be able to detect it with morphine antibodies so that is exactly what he did. He took brain extracts and did radioimmunoassays for morphine and got nothing and he concluded that there can't possibly be an endogenous morphine-like substance in the brain, which was interesting. I thought this is totally wrong but I might not ever be able to prove the opposite.

However Kosterlitz being Kosterlitz, approaching the age of 70 decides he wasn't going to retire. He had to give up the headship of the department but he suggested to me that we make a joint application to the National Institute on Drug Abuse - remember this is the time when there was a great push by Nixon to get involved in drug abuse and the problems of drug abuse and NIDA was founded and all these things were going on. So we wrote up a programme grant, proposing to serve a unit for research on addictive drugs, not based at the clinical school as we were then - we would move down to the preclinical site at Marischall College in the centre of Aberdeen. And we got the grant. Quite extraordinary. The university agreed to give me leave of absence - I could keep my tenure so that I could go back to my job if the thing collpased which was a consideration with a young family.

This did give me the opportunity at last to experiment in a way perhaps I wouldn't have done before. Staying in the university mainstream I might have carried on doing tried and trusted experiments that I knew would yield papers and might actually give me a chair perhaps or at least a promotion. This was an opportunity - it was a clean break. I made it quite clear to Hans I was only doing it because I wanted to search for the endogenous ligand. He wasn't too happy about that.

What was he trying to chase? What was the programme written around ?

The programme was mainly written around looking at whether there was opiate receptor subtypes, looking at the development of tolerance and dependence in isolated tissues and animals. Essentially more of the same as what we were already doing in the department but trying to understand the basic mechanisms underlying tolerance and dependence. When you think about it now I mean it was a very kind of amateurish attempt. There was no way with the tools at one's disposal that one could possibly do that at that time.

But often these agencies fund things because they know this is the area that needs to be funded and they hope that during the course of the project you will develop the tools, isn't that it?

Well that's the hope more or less, yes, but when one looks back and reads the grant application you ask how on earth did we get away with that. There was nothing better at the time. I think ours was as reasonable an approach as anybody's.

I said Hans well look okay I will collaborate with you on the receptor stuff but I really am going to search for the endogenous ligand. No one else need be involved - me and my technician will do the business if you like. "Fair enough", he said, "I don't think you'll have much luck." As it happened we did have luck. It was really incredibly simple in a way once one had decided it was there. You know you have got to be convinced, you really have got to be convinced in science that you're right. This business about the impartial scientist assembling facts in order to disprove a hypothesis is absolute balderdash. Karl Popper could never have been further from the truth. You have got to be convinced

Deluded almost?

Yes and I think most scientists are deluded. I'm sure there are those out there that do pose the questions and go about it in a logical way. But I'm not one of that group. I have to believe in something before I do it and I believed in it. Of course its very dangerous, delusions are dangerous. But I think I was a good enough scientist to recognise that. Now that was the one thing we were very concerned about that even if you did come up with something, how would you prove it really was endogenous. That really worried Hans even before we got any results.

What was the problem ?

Well we were looking for an opiate but we had hundreds of very powerfull opiates in the research unit. You know you could be led a really merry dance if they started to infiltrate into the lab, into the food chain and as it happens morphine is in the food chain, in the same way that cocaine is and the benzodiazepines are.

In broccolli - the benzodiazepines are in broccolli

Well they seem to be everywhere. So that was a concern. It didn't worry me too much but you know we were obviously going to have to do the proper controls. I started out fairly logically looking for various classes of neurotransmitter. Based on the evidence that time, we were going to be looking for a biogenic amine and really got nowhere. I varied the extraction conditions and tried to make them as general as possible and in fact the extraction conditions I settled on eventually were determined by two things. One was the necessity to extract a large quantity of tissue. It is very easy to take one rat brain, for example, and homogenise it in 5 mls of 0.5 molar HCl, add EDTA and ascorbic acid. That's easy but if you're going to homogenise 5kg of brain you end up with an awful lot hydrochloric acid, which is very difficult to get rid of apart from ruining some apparatus as well. So that was a consideration.

We did start off with hydrochloric acid but we got absolutely nowhere. Basically the problem was that we could do extracts of brain and even regional extracts and there were a lot of very depressive substances in there. If you put it on the mouse vas deferens, twitching away nicely there, the mouse vas deferens would just die. You could wash it out but you couldn't show the

critical response which was reversal with naloxone. We got one or two indications. You'd put naloxone on and get a couple of twitches but they would die down again. I'd call Kosterlitz and say "look at that". "Ah, you're deluding yourself" he would say and march off and I'd light my pipe and think about it. You know it did happen - everytime I put that it that happened. It was true but you would never have got any one to accept it. It was clearly there.

Anyway I put all the stuff away over Christmas of 73, closed the place down, stored some extracts in the fridge and then we all went away for Christmas. We came back and I decided to clear out the fridges. My technician, Helen, said "shall we throw these out?". They were negative, they were rat brain, guinea pig brain, rabbit brain and things like that. The research didn't cost much, because when we knew anyone used an animal we would take its brain - they were only interested in testing a blood vessel or something. I said "well wait a minute, lets just check through them once more". So we checked through them and to my astonishment, a couple of the extracts gave the same very fast inhibition but when you put naloxone on this time, it didn't just come back for a couple of twitches, it came back and stayed there. And that was astonishing and it was repeatable I mean I must have dozens of experiments with this extract and a couple of others.

What was the difference between this and previous ones then.

Well I never really followed this up but what I think the problem was is that obviously brain extracts contain a lot of adenosine derivatives and there will be adenosine itself there which is depressant, ADP and ATP, all of which are very depressant. I suspect that plus other substances present in the extract, which had been stored at only 4° not -20, I think they had gone off at 4 degrees. We hadn't meant to keep the extracts. They were other experiments and were put back in the fridge, just out of poor housekeeping really - normally you'd put them in the deep freeze. Now if I had put them in the deep freeze, I think you wouldn't have seen it.

Funny the accidents that can happen and shape things, isn't it?

Absolutely amazing. I have still got the slides. I don't think I've still got the tracings because I had a fire a few years back, which destroyed the original data but I've still got one or two of the slides which show that response. Of course, then, it was relatively easy. Okay you could reproduce those conditions but once you had that activity you knew it was there and you could start to do some chromatography which would have been the next stage anyway. We would have got at it probably logically in the end. But at that point we could move on to chromatography and really it was relatively simple then to purify it up to where you had got an extract that certainly wasn't chemically pure but at least it was pharmacologically pure. You could apply it to the mouse vas deferens and depress the response, give naloxone and the response came right back. It was clearly reversed.

That was quite a sense of achievement. And you could show that there was a fairly small molecule by Sephadex chromatography. I quickly showed it was a peptide although I had been convinced it was an amine - you know self delusion didn't go too far. We did the proper tests, incubating it with some enzymes and they knocked out the activity. To me it was clear that it was a peptide. It was behaving like a peptide on thin layer chromatrography. I had had some experience with peptides working with angiotensin which was a help.

So at that point the problem was really how do we keep the lid on this..

In terms of keeping it ..

Not talking about it. I mean I had told people within the Unit. There were various degrees of excitement. Kosterlitz was certainly excited; he was convinced once he saw a full reversal. The problem was keep a lid on it and also what the hell do we do now? We needed large quantities of brain. You know, I made silly error, one of those absent minded things but I never thought at that time to look at alternative sources of material. It had to be brain or nothing. Now, in retrospect, if I had known more about the field of peptide pharmacology and biochemistry, I would have known that there are people in Sweden, who were extracting huge quantities of intestines from pigs or cows or whatever, and discovering all kinds of peptides in them. It just never occurred to me to try anything else, not at that stage.

So the problem resolved around finding the species of animal that was large enough, that was accessible and it really came down to either the sheep or the pig. There weren't enough cows slaughtered in Aberdeen to give a decent supply. Sheep were very difficult - they've got very thick sculls, with smallish brains and anyway they weren't really slaughtered on a large enough basis. So it was pigs of which they did quite a few in Aberdeen.

I managed to convince the head foreman in the abattoir, which was an old abattoir dating from about the 1700s. When I say it was old, it was open to the skies. Men worked in the open air at benches. There were some covered areas, the killing areas. The pigs and particularly the cows were hung up in stores, in the open air. There were birds hopping around and so on. In fact the place was in such a poor state it was closed down within a year or so. I guess if it had been one of these prissy places, that was always spick and span, they wouldn't have entertained the idea of someone coming in there and dissecting out brains on a bench.

But they were willing to provide pig brains - pig heads we negotiated first of all. As it was I found it was far too difficult to try and break open a pig brain and so that was going to cost me a bottle of whisky a session to get the guy to help me out. Normally what they do is the animal is killed by a bolt, it then goes through a kind of tumble dryer, which acted as a kind of steam bath where the bristles were rubbed off on a rotating drum on a conveyer belt, then it was hooked up onto a conveyer line and it comes to a man who stands with a huge chainsaw, a bit like the Texas chainsaw massacre, the guy stands there and, as the pig comes through, he starts at the rear end and slices the pig until he just reaches the skull and then he stops. Of course what I wanted was for him to carry on going right through the skull so that I can then get in there and scoop the brain out. That disturbed their rhythm, I can't remember why, well it was quite difficult to saw through the skull and I think they also liked to sell them intact.

So anyway, a bottle of whiskey settled it and I was able to get my hands in there and scoop out the brain and then whip it over to the bench and dissect off the cortex and freeze the rest on dry ice. I'd go there at about 5 o'clock in the morning, cycle through the old town, collect the dry ice from the docks first of all, cycle up to the abattoir and work for about 3 hours. Come 8 o'clock get on the bike again - I've still got the bike by the way. I had a carrier on the back - I had pinched a discarded supermarket basket, so that contained the dry ice receptacle which the brains went in on the back of the bike. Back to Marischal College, where I spent the rest of the morning pulverising the brains into a fine powder and then extracting them.

So that was the kind of crude mechanics. One was then into 100s of litres of solvent, large amounts of brain - it became a kind of semi pilot plant operation in laboratories that weren't designed for it of course. That was the real difficulty. That was really quite hard. It took close on

a year to get all that sorted out and to get the chromatography going and all that time of course we were also doing experiments with the materials, studying the distribution in brain, using bioassays to get a fix on it. But really it was at that stage - you know there comes a kind of commitment, its all or nothing. I had stopped all other research, so I wasn't going to be publishing very much, apart from the stuff I did in collaboration with Hans. So you had to be successful or die.

At this point, I almost had a falling out with Kosterlitz. I was certainly very annoyed with him because he had gone across to the States to a meeting of the International Narcotic Research Conference and at the end of this meeting for some reason the discussion had come round to the question of whether there was and endogenous ligand - now we weren't the first to discuss it or even think about it and it was certainly discussed at that conference - but Kosterlitz stood up and said "well in our laboratory, Hughes has now shown that there is an endogenous ligand".

Immediately that caused a furore. It was agreed that they should arrange a further conference, not an INRC conference but a Brain Research Conference, probably to be held in Boston. Kosterlitz came back very pleased with himself and said you are going to be invited to a conference to talk about this and I exploded. I said it was absolutely ridiculous. I think I knew the Americans better than Hans, having worked there.

They're dangerous aren't they?

Incredibly dangerous. Well they're competitive. I don't blame them but I knew how competitive they were. An English group of scientists would say jolly good get on with it old fellow. So I was annoyed to say the least. But the damage was done and I thought I'd better make the best of it. The conference was going to be published in a booklet form; it was called the Neuroscience Research Programme. It was run by a fellow called F O Schmitt at an institute in Boston. The meeting was arranged for May 74. I gave the data - well I went to give the data and before I even got my first slide up - well I put the first slide up showing depression of the twitch - and Goldstein was on his feet saying "is that naloxone reversible; is that naloxone reversible?" I said "well wait for the next slide". I had only met him once before at an INRC conference in Aberdeen and he was obviously very het up. He sat through the rest of the session, unconvinced. He was that kind of man. But obviously other people were convinced, very much so.

What happened was there were a number of what were called rapporteurs, at the conference, meant to write up the review articles. You didn't write the paper - they wrote it up for the book. They were busy writing right through the conference and there were several of these scribes from Snyder's lab. Now, I only heard this story afterwards, there was a guy called Pasternak and a woman called Pert, Candace Pert.

The world knows about Candace, yes

They were supposed to collaborate with the writing up and I heard from Candace that Gavril didn't even stay around for the final minutes of the conference. He certainly wasn't going to be writing anything up because he had disappeared back to the lab in Baltimore to repeat my data but also to try and get a headstart on everyone else.

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Well I don't know about getting it published but he obviously thought well perhaps we can win here, we'll use the binding assay and we'll show that there's a morphine-like substance by the binding assay which Lars Terenius had at the same time. At the same conference Lars had reported similar data to mine using the binding assay. Except he hadn't taken it as far and he wasn't willing to compete with the Americans. He knew how competitive they can get. He said "I'm not going to compete John. If you want to compete you can". I offered to collaborate with him I said "lets work together, you do the binding, I'll do the bioassay, we'll collaborate. He didn't want it. He wanted no part in it. Very interesting.

There are different models of science aren't there? I think it was Phillip Bradley, who was saying to me that schooled in the British school of things, science was a collaborative enterprise and he had his eyes opened by some group in Cambridge whom he found were out to compete and this was a big shock to him.

It was different for me. I mean Terenius was a much more established scientist than I. He had made his reputation in the steroid receptor field. He got into opiates via that. He was one of the first, along with Snyder and with Simon to show receptor binding for which he never got due credit. Pert and Snyder and Terenius and Simon all published in the same year but perhaps unfortunately for Terenius, he was forced by his Head of Department to publish in Acta Physiol Scand, I think because his Head of Department was the editor or something like that. I can't remember where Simon published. But Pert and Snyder published in Science and of course called a press conference at the same time. They knew how to play the game or at least Snyder knew how to play the game.

Whose was the work? Pert or Snyder's?

Pert did the bench work. I mean Snyder has never been anywhere near a bench at all. But there is no doubt in my mind the concept was Snyder's and that Pert would never had got anywhere without Snyder.

There is always tricky. Often quite a few of the breakthroughs are made by the people working on the bench. She would say she was the one who got the idea of using radiolabelled naloxone, without which the breakthrough wouldn't have happened.

Well that's not true because both Terenius and Simon had already shown how to do it using a different methodology. The advantage that Snyder's lab had was that Snyder had been a long time consultant for New England Nuclear. He would say to New England "here's a new biochemical that has just come out I think you should should tritiate this. I think it will sell well. By the way I want first go at it". So he was in a particularly privileged position. And that was the case with naloxone. I'm fairly sure that it was he who suggested that naloxone should be tritiated. So they had this unique tool. I don't think there was any particular merit in their methodology. Once Goldstein had shown that you could get binding, however weak using a particular technology, it was only a question of refining it. Goldstein was the first one.

Ought he not to have been included in the Lasker Prize citation, along with yourself and Hans?

Well the problem with the Lasker Prize was twofold, one was that they tried to split it between two things the opiate receptors and endogenous ligands, which of course were quite separate.

Now obviously Hans and I had worked a lot on the opiate receptors but if they wanted to give it for the binding and the binding alone, then it should have gone to Goldstein, Snyder, Simon and Tyrhennius.

But I understand they only give these things in threes. Candace Pert makes out that that was the reason she was excluded. Have you read the book Apprentice to Genius. How accurate is it?

Reasonably. I think where I do take issue is Pert's situation. We eventually fell out over this. We were reasonably close friends for quite a long time - she had a very extrovert personality very interesting. But she can get a little too heavy and she really went over the top on this. And I'm afraid what she did was inexcusable. She used politics to try and gain for herself a position on the Lasker Prize. She used the women's movement. I mean it was inexcusable. There was not a trace of anti-feminist attitude with any of the people involved in this story. Never was, never has been. That was just a clear political manipulation. Not only that she made incorrect statements at the time - she likened herself to be in the same position as I was. Her relationship to Snyder was the same as my relationship with Kosterlitz.

She was a junior to him, just as you were to Kosterlitz, she said.

It wasn't the case. She was a PhD student, I was an investigator funded in my own right. I wasn't some PhD student, taking orders from Kosterlitz. The work was my design. We were collaborators. Whereas Pert quite clearly was being directed by Snyder. I am afraid PhD students can only have it that way. I'd like to think that PhD students can come up with something novel on their own account will get recognised, I know of people who have been. Brian Josephson here at Cambridge, for his description of the way transistors work and he got the Nobel Prize for that, quite clearly his own work and his own conception and that's a PhD thesis. It wasn't Pert's conception. It was her work at the bench.

A lot of people would feel that the fuss has compromised Snyder, that he may not get the Nobel Prize because of it - because Nobel committees don't like a fuss. What about the fact that his lab trying to scoop your work - you said Pasternak raced back home...

Yes Pasternak did and they were obviously in competition and so were many other groups. I can't blame them. I think there was an element of unfair play if you like in the sense of Pasternak rushing back. There certainly was an inordinate delay in the publication of the booklet from that conference and when it did appear there was work by Pasternak showing that they had an endogenous ligand which was never reported at the actual conference. But it was accepted at the conference that you could add material afterwards, which I think probably everybody did. You could argue, though, that he was adding material that wasn't even thought of at the time. Its water under the bridge but it just demonstrates the competitive power of the Americans. They're going to compete and that shouldn't surprise anyone.

And also the public relations aspect of it. They hold press conferences. They even hold them first and then publish in the journal. How important is that because arguably they do end up being the big names partly for that reason rather than because of the quality of their work

Snyder is very controversial. I know him reasonably well. We have never fallen out, I'm glad to say. Sol is an extremely bright man, an extremely good psychiatrist. He probably could have

made a name for himself in any area, psychiatry or whatever he chose to go into. As it happened he decided to go into competitive lab work after working with Julie Axelrod. What he brought to that was a kind of flair, in sensing out what was interesting and then putting people on that track. That's what he did with Pasternak, Pert and many other people. I think that's what also, harking back to the Pert controversy, that's what weakens her argument because Snyder has had a string of successes - a track record. Whereas actually Pert's record on leaving Snyder was very chequered. In fact it eventually ended in disaster.

I mean she learnt at Snyder's knee was that the way to get on was not actually good experiments, critical experiments but to publicise them. And I can remember at least two press conferences she called, when she was working in NIMH, one was to announce the discovery of Angeldustin, which was the endogenous ligand for the phencyclidine receptor, which died a horrible death and there was another one as well, I can't remember what it was, but there was another press conference. And then of course eventually there was peptide T which she was so convinced in herself that she left the NIH to set up her own company, which I gather has since folded.

Going back to Snyder and publicity, he's played the game. He's played the game brilliantly. Some people hate him for it, some people love him for it but the majority of people know him for it, which probably is the most important thing. There is no doubt about it, I mean I don't know how many millions of scientists there are working around the world, you have only got to look at the millions of papers that are published each year, what differentiates one paper from another? Not very much if you really think about it. So if you can get an edge, a competitive edge, why not use it? It just goes against everything we have been taught in this country. It's not the European way either but it is the American way. Its not only Snyder. He's taken it to possibly the ultimate lengths.

Is there an issue here about citation indices skewing the field. People on this side of the water publish in journals that may not be listed over in the US. I mean could you say that the American's aren't always deliberately not citing people over here but are simply genuinely unaware or work that is being done outside of the US?

We know that's nonsense, don't we? I think there is laziness - that the Americans lay their hands on whatever is close at hand and it tends to be American publications and what they have learned from their colleagues at their own meetings and Europe is a very far away and European representation there is still relatively low.

Plus there is an insular rather lazy attitude and I think plus a degree of xenophobia as well. Of course some nations suffer more than others from this, the French more than anyone else but of course if they will continue to publish in French that really is their problem. It will be interesting to see what happens over the next 10 - 20 years as neuroscience grows in Europe. I don't think it will ever be quite as big as in the States but it will gain. Will there be a more even balance I don't know. I suspect not.

What was the Lasker Prize ceremony like.

Fantastic. I must admit I was and am very naive. When I got a call saying I had won the Lasker Prize, I can't remember how it happened at all now, I think I got a letter from Mary Lasker congratulating me. I thought that's very nice and the money. I must admit I had never heard of it before that. I had had a number of awards anyway and I thought it's nice to get another

award. Fine and there is going to be a trip to New York and there is going to be a few thousand dollars in it, that's very pleasant. It was nice to know that Kosterlitz would be going and see Snyder and then I got a call from Candace Pert. I guess I still didn't twig. She was going on and on about you know she had been excluded. This went on for weeks. At one point I just said "Look Candace, stop this, this is just a prize. Hans has won some that I haven't won, I've won some that he hasn't won. I can't do anything about it". I guess I hadn't appreciated then how the Americans viewed the Lasker. I didn't realise that they recognised it as a premier biological award.

So there was a naivety there. I mean I was soon disabused about that and of course by Candace's antics and then by the press interest and then by the ceremony itself. They put us up at, I think, The St Regis Hotel on 5th Avenue. I had a suite of rooms that I could get lost in. It was actually quite nice because it was the one time that I got to talk to Sol Snyder for 3 hours solid without interruption. We got together in the hotel, in my sitting room and just chatted. It was very interesting. The ceremony itself was real razzmatazz. I shook hands with Edward Kennedy. Whatever you might think of Edward Kennedy this was to my mind the highest I've got in American political circles anyway. I did say hello to Nixon once but didn't shake hands with him. It really was quite something it left you with a sense of gosh they do do these things well.

I have never been that interested in prizes to be honest. The other thing that did astonish me was when these awards start to flow in. It had never actually occurred to me that people would want to reward you. Having the Nobel Prize in the bag was always a joke rather than a realistic idea - well I suppose at the back of your mind there is the hope - its a good enough discovery, they might think about it. But there were all these other awards. It was amazing. Very nice. Some people argue that awards in science are not a good idea I don't know. You can't give an unbiased opinion, once you have won a few. It clearly does lead to some nastiness, there's no doubt about that. And I know there are people in the States that, each time October rolls around, get impossible to live with in the lab. The other thing I hadn't realised is that people actually work towards getting the Nobel Prize in terms of politicking. I don't think you can stop people giving prizes so its a good idea to have as many as we can so at least there's a fair distribution.

The discovery of the enkephalins opened up new perspectives on things. While the antidepressants worked on neurotransmitters that we had previously found in the brain, these were alien drugs, whereas the suggestion with the opiates was that the body produces its own drugs, which made the whole idea of drugs and therapy seem something totally different to what had been before. Before that a drug was a poison, which you hoped to use with art, but after it therapy became a matter of restoring balance rather than introducing poisons. The other thing that changed was the idea that neurotransmission is not all important - that neuromodulation may be as important. Do you want to comment on this?

I think you are right. It opened peoples eyes to a different way of looking at the brain and certainly a different way of looking at drug therapy. There is no doubt about that. Morphine was no longer just an exogenous plant poison, it was something that was tickling the endogenous system and that may well apply to a number of other substances as well. So there was that to it. It opened up a vista as well. We had known about the hypothalamic releasing factors but they were thought of in a very restricted sense and all of a sudden, here is a brain gut peptide that is not restricted at all. And not only that it has a whole pharmacology,

which we knew about because enkephalins didn't come to us new born, virginal, they came to us with a huge pharmacology, a huge fund of therapeutic knowledge and that was really particularly exciting. It suddenly made people realise that there were mechanisms there that we hadn't even dreamt about. And of course within 10 years we identified another 100 peptides in brain. So it started a lot of hares running.

It seems that in some respects the cream of British scientists of your generation, Leslie Iversen, yourself, Geoff Woodruff and a range of others have all opted to go into the industry. Now in Switzerland and Germany, even as far back as 100 years ago, it was very respectable to make a career within the industry. But in this country it hasn't been. It became a little more respectable in the US a wee bit earlier than here and interestingly perhaps one of the companies there in particular who pushed the boat as regards trying to do proper research within the industry was Parke-Davis who set up some of the first industrial research labs. Any comments?

I can only speak for myself in terms of why one moved into industry. I was Professor of Biochemistry at Imperial. The job was becoming less attractive as it was for all academics at that time. Because this was the Thatcher revolution. Although I supported many things Thatcher did, one of the things she did was to my mind quite nonsensical was that she took an axe to the university. It was an indiscriminate axe. I recall well at the time the early retirement programme to try and get the dead wood out.

Which of course would have got rid of people like Kosterlitz. He wouldn't have had any chance would he?

What it did was of course it got rid of the good people. The people who wanted to take early retirement were those who knew they could get another job. In fact I applied for early retirement, I was only 35 at the time. I know from my own department that we lost several good people to early retirement. They knew they had got jobs elsewhere or we had to hire them back in various capacities, whereas the people that I really wanted to get rid of, the people who hadn't done it for 20 years were stuck there. So one was faced with that problem. This idea that there has got to be a linkage between wealth generation and intellectual pursuit, I think is a load of garbage and always has been. No one denies that you have got to generate wealth in this country but the idea that you can take a scientist and somehow harness him in some abstruse way to wealth generation is just barmy.

The only people that can do that are the engineers. If they really wanted to accelerate the wealth generating process, they should have put money into engineering professions and also a commitment to change the way industry thinks about the scientist and particularly about engineers because for too long we have had an industry which has been dominated by arts graduates, who know their Socrates or whatever, which makes them very good at the boardroom, very good at public relations, very good at listening but bloody hopeless when it comes to technological decisions. Until that changes any fiddling about with the university system is not going to achieve anything.

That was one attitude I had. It was also getting more and more difficult to get grants. I was never unsuccessful in getting grants but I was spending most of my time writing grants to support a very large group of 15 to 20 people. Now on top of teaching, administration and other responsibilities for which one is not paid very much, it didn't seem to make sense. At that

juncture in my career, this was 1981, the research was going well but I was open to suggestions.

Parke-Davis came along. The Vice President, who was in charge of research, came and said they were thinking of setting up a research institute in this country, would I be interested in being considered ? Had I seen the advertisement in Nature? No I hadn't seen the advertisement in Nature and I wouldn't have thought of applying if I had have done. They said well perhaps you would like to consider it. I said yes. At that time, they wanted a link with a university and Cambridge was in their mind. It wasn't until '82 that they actually made a deal with Cambridge and then were able to formally offer a job, which gave me time to think about it.

I thought there was nothing to lose and maybe a lot to gain. I was being offered a chance to build an institute from scratch, in some ways like what we did in Aberdeen but in a slightly grander form this time. There was going to be the academic dimension, so it was attractive that I wasn't going to have to break the ties completely. Quite frankly the idea of developing drugs, discovering drugs was intellectually challenging and very exciting. I was trained as a pharmacologist and here was the opportunity to do something I couldn't do in academia, to get chemists and biologists together to work on a common problem and they were going to let me choose my own problem as well.

They didn't ask me to come a run a research institute and tell me "and this is what you will be doing", they asked me well what would you do. I wanted to work on neuropeptides. Neuropeptides were the coming thing. I mean this is 10 years after enkephalins and after Hokfelt's and other peoples work. Peptides were there but no one had ever done anything in terms of developing a useful therapeutic agent from them, by and large. So there was an intellectual challenge, a commercial challenge and there was the therapeutic challenge.

It was just really the question of deciding where one was going to fight one's battles, what area were you going to choose. I don't think I had anticipated quite how challenging it was. I knew the industry would want its pound of flesh. I wasn't naive in that sense. I had worked with Parke-Davis many many years previously, as an undergraduate. I took a year off when I was at London University to work as a technician at their Hounslow Laboratories, which was subsequently closed down when Parke-Davis merged with Warner-Lambert so I was well aware of the pressures in industry and I knew that they weren't going to sink many tens of millions of pounds here without expecting something back. My favourite expression is that the life of a research director is fairly short and can be brutish so enjoy it while you can.

The kind of comment one sometimes hears from others, who may just be jealous, is that scientists can do science but they can't really discover drugs and there is inevitably this tension if a company spends a lot of money on bringing in the best scientists who tackle interesting problems but don't necesarily deliver drugs which clashes with the corporate raison d'etre. Is there a clash between being a good scientist and being a person who knows how to actually develop a drug. Are the two compatible?

I can't agree that there is a clash. I mean I hope I'm a good scientist and I hope that I'm actually quite good at developing drugs. What I would say is that being a good scientist doesn't guarantee that you are going to be good at developing drugs but the two are certainly not incompatible. You have got to think in a different way. You have got to rise to this particular intellectual challenge, which consists by and large of putting a lot of different strands of technology and people together.

I mean discovering the drug is actually the smallest part. It is actually then what you do with it and how you stay with it. We have a particular drug that we have had in development for eight years now and one we could have given up on many times. There have been disappointments. It has gone into a clinical trial and it has not fulfilled its potential but we have kept at it. We have kept doing basic research with it, we have kept it alive within the company. The idea is to get the compound into man. Just because it doesn't appear to work for the original indication doesn't mean we should drop it. Lets look at the other possibilities. We have done that with this compound and we are now going in a completely new direction.

The classic case, I suppose, are all the compounds active on the 5HT system which were developed as antihypertensives, because they are antihypertensive in the rat, but not in man. In humans though they actually do do a whole lot of other things.

It is very foolish to think that you can go in a straight line in drug development, very foolish indeed. With the state of pre-clinical science, particularly in neuropharmacology and psychopharmacology, it is impossible to predict what is going to happen in man. All you can say is given the best of circumstances, we think this drug will have this particular group of properties and that it may be useful in this particular set of conditions. However, until we get it into man and we then begin to evaluate its psychopharmacological profile we really won't know where we are going. But we can then feed that data back to pre-clinical investigations once more, so its a two-way process -its not a straight arrow. Time might be a straight arrow but the drug development process is not.

Isn't there this problem at the moment that we seem to have hit - Alec Coppen put something of this in terms of psychopharmacology being like trying to hunt for oil - to date even though we've got very sophisticated geology, the best way to find oil is to dig oil wells and in terms of pharmacology its to give drugs. In the 60s we were able to give drugs to people but now we can't with the same abandon. The increasingly sophisticated pre-clinical work gives people the impression that all the science has been done by the time a drug comes to man and we fail to appreciate that so much more needs to be done once it gets to man. But the problems of doing that work in humans seem to be increasing the whole time. Its very difficult to insure work with healthy volunteers for instance outside the industry.

Its a bit easier in this country than in others particularly in the States. But you only get one bite of the cherry even in industry. You have got to get it right and that's the art of the preclinical sciences - to try and choose your best ligand to go into man with and hopefully keep it there long enough that you get it used so that even if it is not the ideal drug you can have another one waiting in the wings once you have got clinical evidence of some sort. Its a pity you can't go into man in that way anymore.

One of the other problems I think is that no one discovers drugs the old way any longer by putting them into animals either. They go into a binding assay, they go into an enzyme assay, they go into a cell line or whatever but no one does a whole animal screen.

Do you think this is wrong?

Is it wrong ? Not from industry point of view because clearly that was not a very efficient way of doing things but by God did it discover drugs. I am reminded about another drug that we are working on that was discovered precisely that way. Its pharmacology is well described, or at

least people think its well described but we are now looking at it at a molecular level and find its doing something quite unexpected, which is going to lead us back now, I hope, to a new line of drug discovery entirely. We can now go back and re-invent that drug in a different form for different uses.

So yes there is a place for that kind of pharmacology. I don't know where you do it - I mean it would be more than my job would be worth to suggest to the company that we should go back to taking compounds and randomly putting them into a CNS screen or something like. I don't know how you do it. The way Woodruff and I try to do it is that we look around and see what there is in the literature and try and put two and two together. There are things that turn up that the original discoverers don't spot themselves.

On that line one of the other interesting things about a psychopharmacology meeting these days is the secrecy issue - whereby there are things that industry scientists can't discuss because of patent issues etc.

Its business. I don't believe that there is much that we can't discusss - the one thing is clinical results and that's a shame. It is very difficult to present early clinical data - I mean you are just giving away too much to the opposition. Its an intensely competitive area. On the preclinical side Glaxo, for instance, seemed to be pursuing an open policy a few years ago but now they seemed to have become more secretive again as far as I can see. There is another company I can think, whose Research Director told me that they now deliberately don't publish on anything. They may be right because you know we are all travelling along roughly similar parallel lines - it is luck by and large whether you get to a chemical entity first. Once you get there may be it is a mistake to give it away too soon.

So a sense of balance is needed. There is this terrible balance all the time of commercial advantage against the disadvantage of switching off your scientists. The last thing I want to do is switch these young people off. They are here to discover drugs. They are just as interested in discovering drugs as I am, I know that. Coming back to what I said at the beginning, scientists only do what they do because they are interested. Its like a stamp collector - he collects British Empire because he likes British Empire stamps, not for any logical reason. Its the same with these guys - so you have got to harness their inquisitiveness, direct it to some extent but not too much and that's the fascinating bit of the business. Its not easy to do.

So you are as interested in the art of management as much as anything else.

I try and do both. I still have an active research programme of my own but my main responsibility here is to make sure this place works. And most of all to these people, making sure they keep their job and they will only keep their job if they discover drugs. That's the hard facts of the world we live in. In the same way as academics only keep their job, if they keep on publishing. No it is intellectually challenging. I don't subscribe to any fancy management theories - they come and go the whole time. It comes down to individuals and the way they handle things in the end; there's no particular role model, no pattern that anyone can follow because every situation is different.

Is industry a very conservative force within psychopharmacology? For instance once it was shown that many of the early antidepressants blocked reuptake, industry kept on making reuptake blockers rather than going out and finding out something new about antidepressants ?

By and large it is bound to be conservative because of commercial exigencies but also, and I have to say this, because the scientists who work in industry are not the pick of the bunch. There is competent science but they don't do innovative science. The incentive to take risks is not there because if you take risks it means you stick your neck out. Now I'm the kind of guy who takes risks. I can afford to because I'm not bothered if someone sacks me, I know I'll get another job. Now if you're a middling scientist in a middling company are you going to stick your neck out for a drug you can't be certain will work? Time and time again people play it safe. Rather than say bring a line of compounds up for consideration for clinical development, they stall. They say "well perhaps we ought to look at this and this." I know discovery teams that have got ten or more years working on a particular line of discovery and never bringing anything to the point where it would be put under the microscope or even less into patients.

Now it may not be deliberate. They may not even be conscious that they are doing it. But I can see it happening and to me the mechanism is obvious - they feel uneasy about being challenged. That was the other thing I noticed when I came into the industry. I have adjusted since but I was brought up in the hurly burly of the British Pharmacological Society.

The British Pharmacological Society really is cut and thrust.

Yes, you were brought up to ask questions and give as good as you got and fair enough if you are going to get up and give results you have got to be prepared to defend them. And that's a good British tradition. The Americans do it somewhat differently. They tend not to challenge openly. Within the industry they certainly do it differently. They don't like this cut and thrust; they are not used to academic exchanges; they don't like it and one has to be carefull of upsetting sensibilities. That was a difficult one to get hold of and by and large that is why this place was set up or I like to think it was. It wasn't set up to be a mirror image of Ann Arbor, which is our main research headquarters. It was deliberately set up by the Vice President at that time because he thought it would be good to do something different elsewhere and until someone tells me different I consider that's my remit. To be a bit of an iconoclast, to stick my neck out and to do things differently. If you can't take risks here you won't be able to anywhere.

But to come back to what I said earlier, I have to balance the fact that we're a mature organisation, after all we've been here eleven years now, against the fact that I have a large number of people here who depend on me to some extent and certainly Parke-Davis for their jobs. So I hope we are not heading down a pathway where oh my gosh we'd better not do that because that's my paypacket at stake but equally we have to be sensible.

Sometimes industry though can all of a sudden create a field - I mean they created psychopharmacology.

Who else could have done it. Clinicians couldn't. They needed the Chemistry. At the end of the day unless you have the Chemistry you're not going to get anywhere.

How have things changed in the last 10 - 20 years?

There have been tremendous changes. What used to be the old classical approach, which is what I was trained in has almost completely gone by the board. I'm not sure you can distinguish a psychopharmacologist from any other kind of neuroscientist these days. Everyone uses molecular techniques, everyone is asking roughly the same kind of questions.

The role of psychology is an interesting one. I sometimes wonder if the gulf there is much greater than perhaps we suspect. Psychologists seem by and large to be asking different questions from the psychopharmacologists.

Do you think there is a risk of going too much down the neuro-sciences route?

No. You have got to follow where the science is going.

But how can anyone, at least anyone working clinically these days, keep up with the explosion of knowledge within the neurosciences ?

They have to focus on a specific area - obsessive-compulsive disorder or whatever.

But then you don't make the bridge across areas. Are we at a stage where we are going to lose the possibility of having people who can make the connections across diverse areas? who can see the implications of discoveries in one area for development in another? The kind of link that you made between the nictitating membrance and the vas deferens - you'll get people who are just vas deferentologists

Well I think there will always be individuals who can make these connections. And after all cardiologists don't have a lot in common with urologists these days, do they? There has got to be a linking process, you're right. But one thing I am convinced of is that we are only at the start of the psychopharmacological revolution.

So what comes next. We had that breakthrough in the 50s and 60s when all the major groups of drugs were discovered ...

And nothing since. I think what you are going to see is the true second revolution. Serotonin uptake inhibitors are all very nice but they really are variations on a theme and however useful they may be it is not that significant an advance. No you are going to see the true treatment of psychosis, the treatment of disorders like obsessive-compulsive disorder in a rational way that goes to the heart of what is involved. I think you are going to see a lot of fragmentation of psychiatric disease

There is going to be a real challenge, I don't know when its going to come, to medical ethicists, to industry, to regulatory authorities when the first drug that can truly improve memory arrives. I'm not talking about anti-Alzheimer drugs, I'm talking about true cognitive enhancers - nootropics or whatever you like to call them. It will happen as sure as eggs are eggs - someone is going to discover a way of either improving the learning process or improving the retention process. How are you going to control that? Would you even want to control it? You are then into a brand new era, aren't you? You could then actually say that a psychopharmacologist, not only is going to be able to cure some of the worst ills of mankind, but he could actually advance the cause of mankind. I don't think anyone could rationally argue that it would not be a good thing to improve learning or memory ?

In the 60s the public were all for these new drugs that were coming out but more recently there has been this great concern about drugs and even though the drugs we are producing are safer and safer there seems to be more and more concern about what can be trivial side-effects or a feeling which people seem to have now got that they are born with a warranty - that nothing should go wrong for them.

The no-fault environment. I guess that comes out of the States to some extent. There has been a whole sea-change. People now expect, as of right, and unrealistically expect that everything is going to be perfect. Americans want to live forever and want to remain beautiful forever. I guess the Europeans will go that way - they're always ten years behind.

Also there is an unrealism about in the sense that people don't understand science. By and large people are so ignorant about science and they don't understand the problems and the difficulties and they forget also what it was like before they had these drugs.

The folk memory is so short.

Terribly short. Of course we can cure that - haven't we got penicillins, haven't we got phenothiazines, we can do this, this and this. It is the same argument that is used by the animal liberationists and the other ecologists or the rights movements - we don't need to do it, we don't need to continue to do dissection of animals, why should we do anatomy? Its all there, it has all been done and its all on file, on computer file no less.

What these people don't realise is that science is built by accretion of not only what other people have done but you have to learn manually from those people. Take John Vane - he passed on a little bit of his knowledge to me and hopefully I will pass on a bit of mine to my students. If you have a clear break and you no longer have that experimental connection, the practical connection, the hands on connection, if you no longer have that then the students might as well be working on their own trying to reinvent the wheel. That's what will happen eventually. It will be like the Greeks - it will all be theory and no practice and you know what happened to the Greeks.

What about the climate though in terms of difficulties in bringing drugs to the market because they have to be whiter than white.

Inevitable. What has saved us so far is technical advances. We can now do things we couldn't do 10 years or even 5 years ago and hopefully technical advances will keep up with the demands the regulatory agencies place on us. There will still be no substitute for being smart - that's what it comes down to and it will be the smart people and the smart companies who will survive.

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