THE PSYCHOPHARMACOLOGY OF SEX

I usually begin with how do people get into the field they end up in but I'm just not quite sure where to start with you ?
I don't know why I went into medicine. From the age of about 8 I wanted to be a doctor and nothing persuaded me not be in fact, although many people tried to put me off. I was the first doctor in the family.

Where did you train?
I trained at the old Charing Cross, in the Strand, between 1962 and1967. I had my first job in sexual medicine there with John Randall who was a consultant psychiatrist who ran the gender services for Charing Cross hospital. In those days, homosexuality was still illegal and I worked as an SHO in a unit where we treated homosexuals by aversion therapy.

The agents used then were mainly apomorphine to produce vomiting?
Yes. We used apomorphine and on a few patients we used electric shock, but mainly we used apomorphine intravenously to make these people sick. Obviously there were no videos and we had to show them slides.

This was a very behavioural programme?
Yes. Interestingly, the slides that we showed these men that got them aroused I'm sure these days would not have any effect what so ever on them. I think people have become habituated to erotica in that respect. I don't think the treatment worked, but it was an easier option for these patients or perhaps more accurately these people to go through a treatment programme than to go to prison.

Then when I later did a house job in North Devon, I did an SHO job in obstetrics and gynaecology and was responsible for the infertility services for north Devon. Here again I started seeing a number of patients with sexual problems and had no one to refer them to. So I thought then that sexual medicine might well be something to consider although there wasn't even the term sexual medicine then. And perhaps because of that I ended up going into general practice first.

The problems that you were seeing in these women were dyspareunia?
Well yes we were seeing dyspareunia, a lot of anorgasmia, and people that really had got conflict in their sexual relationship and a conflict in their non sexual relationships really. But in those days, in the late 60s, we really didn't have a very good idea of the nature of sexual problems. I mean female problems were generally classified as frigidity, which covered everything and male problems were impotence, which again covered all types of male problems.

Then I went into general practice because my belief is that everyone should go into general practice for a period of time. Because I think it rounds off ones education. But I had no intention of staying in general practice for the rest of my

life. While there, in Bideford in North Devon, I was again seeing a lot of patients with sexual problems both in general practice and in also in a clinical assistanceship in obstetrics and gynaecology that I had. And it was then decided that this would be a career for me.

But there wasn't a career structure. Things were very primitive. The Brooke Advisory Service was just beginning to set itself up. This operated mainly from the counselling point of view and marriage guidance was functional - more interested in relationship issues than sexual problems. When I looked around, there was really no career structure or formal training programme for the type of medicine that I wanted to practice, which was the more medical aspect of treating sexual problems.

What was actually known about at that point of time, in terms of what drugs could be used for what conditions?
Well there were some drugs being used such as yohimbine. This was first discovered in 1947, or at least the first paper was published about 1947. It was being used in combination with strychnine, methyltestosterone and a centrally acting stimulant called pemoline, in beautiful little gold milled pills called Protozan Forte.

That's quite a combination!
It was quite a combination actually but it had some justification I think as I look back on it now. Methyl testosterone was probably was not absorbed - it has a very erratic absorption and large first-pass metabolism, so I don't how much testosterone these people were getting. Strychnine probably had some effect on neuronal transmission. We were using it for erection problems essentially, and a lot of men claimed that it really worked. Now looking back on it we know that there is about a 30% placebo response rate in the treatment of erectile dysfunction, and it may have been the 30% that we were seeing that was responding. At that time there really was no formal trials of this compound.

Protozan Forte remained prescribably up to the seventies. But after a period of time of using these gold balls, gold milling became too expensive and the pharmaceutical company that was involved, called Medo Chemicals, started producing the pills in orange coating as opposed to gold coating and the efficacy dropped off very dramatically. Clearly the men liked the gold milled pills and as soon as we changed, they claimed it wasn't as effective, which points to a placebo effect more than anything else.

In terms of Yohimbine what was it thought to be doing? Its one of those almost folklore pills
It was characterised as an adrenergic blocker at first and then sometime later when alpha adrenoceptors were broken down into 1 and 2, it became an alpha-2 agent. There was no toxicology on yohimbine then and there still isn't.

There did seem to be a indication of placebo effect since the change in formulation of Protozan Forte caused men to say that it was less effective. People did start doing some clinical trials on yohimbine. A urologist called El Moralis who was working in Kingston, Ontario, did some trials where they showed a slight improvement or benefit of yohimbine over placebo particularly in people with less organic erectile dysfunction. We did a UK four centre study which showed a modest benefit over placebo with yohimbine in men with erectile dysfunction through all causes. In those days, we really weren't investigating the cause of erectile dysfunction intensively.

The main problem about yohimbine was the lack of any safety data, and there still isn't any. With the setting up of the Dunlop committee, yohimbine lost its license, because of lack of safety and efficacy data. But it was being used quite frequently up until the introduction of Viagra and in the year before Viagra was launched, yohimbine was the most frequently prescribed drug by American urologists. More frequent than antibiotics or any other class of drugs. It had a large following

Well that's enormous
That's right. The revenue was really quite marked. But no company wanted to do the tolerability and the toxicology studies because it was off patent and its just not commercially viable to do that if its off patent because anyone could then market it.

But the animal studies on yohimbine were really quite encouraging, particularly rat studies where it showed that where elderly male rats showed a decline in sexual functioning, if they were given yohimbine it almost rejuvenated their sexual activity. Many animal pharmacologists saw this and started to think in terms of modelling a novel compound on the pharmacological properties of yohimbine.

Now yohimbine is quite a dirty drug. We know it's an alpha 2 adrenoreceptor antagonist but it also is has serotonergic activity and activity on other receptor sites. What pharmaceutical companies did was to try to develop drugs that were alpha 2 blocking drugs. Now before companies started really looking at this, I was working for Glaxo who had an alpha 2 blocking drug, fluperoxan, on the shelf, a novel compound, which they were going to evaluate in a variety of different clinical conditions. I could not get them to look at erectile dysfunction as a viable and worthwhile end point target.

The drug remained on the shelf for about five or six years, but then Syntex developed a new alpha 2 adrenoceptor antagonist called delequamine um and they put this into clinical trials - I was running their trials for them - and this induced Glaxo to set up trials on fluparoxan. Now delequamine was a very potent drug, which in early studies certainly enhanced erectile activity in men. It went into clinical trials where there was a modest benefit over placebo probably due to

inadequate dose level. There were plans to repeat the studies with higher doses, but Syntex was brought out by Roche and Roche did not want to be involved in the sexual arena. So all work on delequamine stopped.

Fluparoxan then went into clinical trials in erectile dysfunction. This was in the mid to late 80s. Again it showed a modest effect over placebo, but the company was feeling quite insecure. Glaxo are a traditional British company, and they took the commercial decision, not based on any medical facts or pharmacological facts, not to progress fluparoxan.

The reasons for that were what?
Ah they did not appreciate the size of the market or the potential size of the market. I think there was a lot of insecurity within the company looking at a drug for a sexual indication. Reckitt and Colman had another alpha 2 blocking drug that went into clinical trial, actually just before delequamine, called idazoxan. That was also taken out of clinical trial, after one publication on it in the treatment of erectile dysfunction, which wasn't all that good. It was seemingly causing an unacceptable of adverse effects, so that came out of clinical trial. And in fact the clinical trials with idazoxan were not pharmaceutical company led – they were investigator led, and it was a psychiatrist called ??

And that really saw the end of the alpha 2 blocking drugs. I still believe however that this class of drug has a potential for use.

For what precisely?
For erectile dysfunction and maybe arousal dysfunction in women. There's been no evaluation of the alpha 2 adrenergic agents in women to date. Nothing that has been published anyway.

Now in the sixties we were also using drugs for the treatment of premature ejaculation - the antidepressants. It had been noted that one of the common side effects of antidepressant drugs was delayed ejaculation. This was probably first noticed in the early sixties with the monoamine oxidase inhibitors. After that Anafranil, or clomipramine, became available and that seemed to have possibly an equivalent ejaculation delaying effect as the monoamine oxidase inhibitors but without the dietary restrictions and all the other adverse effects that one has with MAOIs.

In those days Anafranil was marketed by Geigy Pharmaceuticals, and it was their medical director, George Beaumont, who pushed this forward. He was very keen to get this developed as a treatment for premature ejaculation but I understand that he had great difficulties in convincing his company that this was a viable and respectable indication.

At that time George was running every three months a group. Not really a seminar group but a research group of people interested in the field. There were

about 10 or 12 people who George took away at weekends to discuss Anafranil in premature ejaculation and other drugs with some potential for treating sexual problems.

That group must have been pretty well the whole field in the UK at the time – who was in the group?
There was John Bancroft of course. And Barry Everitt, an anatomist from Cambridge. Ivor Mills from Cambridge, who was very fixed on nortriptyline, for his anorexic patients in those days. I remember him using it for treating it for sexual problems because he noticed that some of his anorexic patients had increases in sexual function when they had nortriptyline treatment. I suspect this was just treating anorexia rather than a specific effect of nortriptyline. There was a woman called Beverly Moyse who was a psychiatrist in Hull. (Who Else?)

They were very useful meetings.

Talking about premature ejaculation, following on from Anafranil of course, were the selective serotonin reuptake inhibitors. I guess they are the drugs of choice now for this indication. But none has been licensed as yet, and there is a good reason for this. If you license a drug for premature ejaculation it emphasises the ejaculation delaying effect and each company claims that their drug is cleaner than the other drugs in sparing sexual function. So there is a commercial danger in developing these drugs, although I believe there are some companies now that are looking at SSRIs purely for their ejaculatory indication. And that would make sense, separating it from the antidepressant effect.

As far back as 1991 or thereabouts, some of the companies were very much aware of the size of the market - I heard figures quoted that up to one third of men have a premature ejaculation problem, that's a vast market.
Yes its bigger than the Viagra market for erectile dysfunction. But the whole philosophy of treating sexual problems in those days was behavioural, and in fact it took quite a lot of bravery to start prescribing drugs without the behavioural context.

Why the bravery?
I think it was brave, because it was almost breaking new ground. Premature ejaculation was thought to be a purely psychological or behavioural effect,

To be treated by Masters and Johnson type approaches
And therefore the treatment should be behavioural. I know when I spoke at meetings back in the seventies on the use of drugs in sexual problems I was often shouted down and told that you know that this is not the right to be doing

What are the feelings or the issues involved?
Well I think the feeling among a lot of the therapists, especially the more behaviourally orientated psychologists and psychiatrists, were that drugs were

beginning to medicalize sexual problems and that sexual function in general was becoming medicalised. There was a lot of resistance to this

I think it was really based on a lack of understanding of the pathophysiology of these problems. I think this attitude is one reason that really delayed drug development in the treatment of sexual problems. And we still see it now actually. If I go to meetings and present data on Viagra or whatever, there's still a small nucleus in the audience that talk out about using these drugs, that one really should be using behavioural approaches in the first instance. My own feeling is that we should be using behavioural therapy in addition to pharmacotherapy. I think we should solve any psychological issues before prescribing, but that's just not practical in today's world.

The other drug treatment for premature ejaculation, which started in about 1943-44 was local anaesthetics applied to the glans. The first one was lignocaine and some people presented very large series of premature ejaculations treated in this way. Urologists are still using local anaesthetics but its not something I subscribe to myself because the evidence that premature ejaculators have a hypersensitivity of their glans is really quite thin. There are one or two studies showing that they do have an increased sensitivity but most studies have really disputed that.

But if it works?
Well I'm not sure if it does work. You see some of the remedies for premature ejaculation that you can buy at sex shops have a local anaesthetic in them. In clinics the issue may be that we are not seeing the successes with these treatments - we may be only seeing the failures and it may be working but that's not clear. We see lots of people in our clinics who have been seen by urologists in the past and have had local anaesthetic and who still have a problem.

There are risks of course with sensitisation and also risks anaesthetising the partner. There was a proprietary product containing lignocaine called Stud 100, an awful name, but this compound was actually licensed by the Medicines Control Agency for the treatment of premature ejaculation. It's a lignocaine spray.

You don't see that in the British National Formulary!
You don't see it in the BNF but it's available in some pharmacies. I actually wrote the submission to the CSM for it to get it licensed, both here and in Australia. This was around 1990. It delivers 7 mg of lignocaine every spray, and you give 2 sprays to the penis. There is very little data to support its use and I'm surprised it ever got a license.

That's about all with pharmacological treatments of premature ejaculation. Viagra is being used but I don't personally believe it's the right treatment for premature

ejaculation. Some people are using it for premature ejaculation mainly to allow the man to have a second erection after the first ejaculation

The opposite of premature ejaculation is retarded ejaculation, and this is a very real problem. It's not as common as premature ejaculation by any means but it's a difficult problem to treat. And one cause of retarded ejaculation is the use of antidepressant drugs. There have been several case reports suggesting that by giving patients an additional drug to their antidepressant, you can overcome problems such as this. We've published cases on using cyproheptadine, which seemed quite effective. Other people have used bethanecol, which is a cholinergic drug. Yohimbine has been used, and now Viagra is being used, but I'm not really sure why it should work in retarded ejaculation. We do need a drug actually to treat retarded ejaculation,

Would buspirone or cyproheptadine or trazodone on their own work for problems other than drug induced problems?
We've tried cyproheptadine on its own, and I can't say its been effective. It's worked on one or two people but not the majority of people.

Animal work though seems to suggest that the 5HT-1 agonists and 5HT-2 antagonists can bring orgasm forward
Well ejaculation forward

Are orgasm and ejaculation the same or not?
I think they are two different processes actually. I'm not sure if animals actually have orgasms. Cyproheptadine has worked in some men with retarded ejaculation but not in others.

One of the things going the rounds lately is this. The original story about the SSRIs was that they led to delayed orgasm or ejaculation or whatever but that this happened while you're on the drug and cleared up when it was halted. But recently there's a suggestion that problems may clear up for 99% of people but not for everyone. In some cases, problems may persist after you halt the drug. Is this a possibility?
My feelings of that are actually that these are probably problems that pre dated the onset of the antidepressant drug, that were not diagnosed and they are using the drug as an excuse for a pre-existing problem.

It's difficult to imagine how you could get a continuing problem unless it's a fear of failure - because they couldn't ejaculate on the drug they get in addition to the pharmacological interference with ejaculatory system they get a secondary psychological problem, and the psychological problem persists after the drugs have been withdrawn.

One of the other antidepressants we should mention is buproprion. This is both a dopamine reuptake inhibitor and noradrenergic reuptake inhibitor and there has

been quite a lot of interest in it recently. It's been used to reverse psychotropic induced ejaculatory and orgasmic dysfunction, and also to reverse erectile problems in men who are on antidepressant treatment. But it is now being looked at as a treatment in its own right. It seems very good for women with loss of sexual drive and orgasmic dysfunction. It has been studied in some trials, which although poorly conducted, and poorly designed, and the results have been quite encouraging. The studies have the methodological weakness of having a placebo run in and then switching the patients blindly into active treatment. They then demonstrate an improvement on that switch. No one has done a parallel group study, which you really need

But the person that seems to be pushing this is Taylor Seagraves. He's a professor of psychiatry in Cleveland Ohio, a delightful man who's done quite a lot of work on drugs in the treatment of sexual problems over the years. So I think we are going to hear more about buproprion.

The most potent drug that has ever been in clinical trials for the stimulation of sexual drive in women was also a dopamine agonist called quinelirone. This was in trials in the late eighties, in America. They recruited large numbers of women and it certainly increased their sexual drive but they were all sick with the dopamine agonist. So that was taken out of development. But there is now interest in trying to separate out the various dopaminergic receptors to find, to try and see if the receptors involved in the sexual responses are similar to those in emetic responses.

Just on that point, when you were giving apomorphine for aversion therapy you gave it in doses to make people sick but could it also have increased libido and been counter-productive to therapy
We now know lower doses would certainly have enhanced erectile activity, and that was not known at the time. And it was quite strange actually, because I remember commenting to John Randall in those days that some of these men were getting more excited,

And he said no no
Precisely. But we were using massive doses so you wouldn't expect a marked increase because it has bell shaped dose response curve on the sexual side. Apomorphine though now has a license for the treatment of erectile dysfunction but the clinical trials on apomorphine have shown it really not to increase sexual drive. I'm not convinced about this. I think the instruments we are using to measure sexual drive are probably insensitive. A centrally acting dopamine drug should increase sexual drive.

We saw this when L Dopa first became available. People with Parkinson's Disease who had been treated with l dopa reported increased sexual drive. In those days, it was explained very much in terms of relief of Parkinsonian symptoms and therefore they felt better, and therefore they had sexual drive, but

that really didn't explain the effect of L dopa in animals who showed an enhancement of sexual responses. I think that was a true pharmacological effect.

Now we are not seeing this with apomorphine in the treatment of erectile dysfunction primarily, I suspect, because of a weakness of the instruments being used. My own feeling is that with Viagra, we should also see an increase in sexual drive in men but not through a pharmacological effect but rather because they have got their sexual functioning back. But that hasn't come out in any of the trials either and again I think it emphasises the weakness of the instruments that they are using.

So we've talked about dopamine agonists. Some patients actually seem to improve their sexual functioning on very simple dopamine agonists such as bromocriptine. I've used bromocriptine for the treatment of sexual dysfunction associated with renal failure and was really quite impressed with its effect. It is not a panacea by any means, but anecdotally it seems to better than doing nothing. I think during the next few years we are going to see more selective dopamine agonists becoming available for clinical trials, mainly for sexual drive disorders.

Can we go back to the sixties, which were a time when attitudes were opening up etc the pill had just come on stream. Did the changing climate play any part in your interest to go into this area of medicine?
I don't think it did no. The swinging sixties were a time when people were focused very much on sex, but I don't really think that really influenced my decision to go in for this area.

What impact did the pill have on the whole thing?
I qualified in 67 and the pill was just becoming freely available, so I really didn't practice before in the pre-pill era, so I'm not in a position to assess any change. I think what it did do however was to enable women for the first time to think about their own sexuality. Because the problem that we were seeing primarily in women in the late sixties was anorgasmia and I think women were then beginning to realise that they should be getting more out of sex than they were, and they presented with anorgasmia. The commonest problem now is loss of sexual drive and we don't see a lot of anorgasmia except when it's secondary to psychotropic drug treatment.

You don't think that the change in the word might be a change in the word rather than a change in the problem? If all complaints in the 60s were put down to the inability to have an orgasm, perhaps they had loss of sexual desire then also.
I see what you mean. I'm just trying to think of the best way of answering it. I think anorgasmia was a problem then essentially because women were coming out of the sexual dark ages where masturbation was frowned upon. They hadn't experimented with themselves, as it were. And I think we see much less

anorgasmia now because first of all, although masturbation is still frowned upon in some areas, women feel much more comfortable about masturbating and secondly because women's magazines have told women how to have an orgasm. But women's magazines can't tell women necessarily how to increase their sex drive. And so we are seeing less anorgasmia more loss of sex drive.

I'm sure in the sixties there were people with loss of sex drive but they just didn't come to the clinic. I don't think anorgasmia was a symptom of loss of sexual drive, I think It was a symptom in its own right. Once you helped these people to have an orgasm they were happy and content. But whatever clinic for women you look at these days, loss of sexual drive is the most frequently presented problem. And that's really where we need drugs at the moment.

My feeling about the female drive is that, and our own data shows it, at least 33%, a third of women, never experience any spontaneous drive. I think this is a women's physiological lot. Biologically she only needs to feel sexual drive once a month. I think women are now trying to get more out of their sexuality than perhaps their biology allows them to. Feminists would perhaps not like to hear somebody say that. And I think what we are seeing in the clinic with the loss of sexual drive, is loss of proactive sexuality. In other words these people are not willing to initiate sex, but if offered it they are quite happy to continue. And I do believe that's typical of female physiology for many women.

Typical – you said one third?
Well 33% never had any spontaneous sexual need or drive. We have using for many years testosterone in these women

Now when you have a group of women like that and you give them drugs like, quinelerone, what happens? Is it just the group that have the sexual drive to begin who get more, or is it the group who don't have any to begin with that get some
It's both actually. But its by no means a universal response. When we are treating sexual drive disorders, either psychologically or pharmacologically or hormonally, the responses are really quite disappointing with the exception of those women in who you demonstrate a physical problem, particularly low androgen level. These women respond very well to androgen replacement.

The big problem there is that we don't know what the normal level for testosterone is for women. We know what the laboratory level is but we don't know how that reading relates to what women really need. One of the studies we did was to take a group of women who never had any sexual drive throughout their lives and compared them with age matched women who had what one could describe as normal sexual drive - they would develop sexual fantasies, they needed sex. In the women with no drive, the free testosterone level was lower than in the women with drive but even in the low or absent drive group none of the levels were outside the normal laboratory range

This makes you think the normal range is inappropriate. Testosterone has been used in the treatment of absence of sexual drive in women, since the 1940's when a gynaecologist called Greenblatt in the States noticed that when he remove the adrenal gland and the ovaries from women with cancer they lost their sexual drive, and then when he gave them testosterone their sexual drive returned. I think these women had a lot of reasons for losing their sexual drive apart from being androgen deficient, but that really started people being interested in androgen replacement for use in women, along with one HRT product called tivolone, which has androgenic activity and has a license for increasing sexual drive in post menopausal women.

There is a lot of work in America at the moment looking at low dose testosterone patches for treating women with low sexual drive. There is also of interest in America in adrenal androgens, such as DHEA, and although there's been few good trials a lot of the uncontrolled trials and the anecdotal experience suggests that DHEA is probably as effective if not more effective than testosterone. It is of course a testosterone precursor. I think it's a question of watching this space and see what happens with these. DHEA of course used to be available in health food shops in the UK but its no longer available.

It can still be got in the US.
It can be got in the US 50mg tablets, yes. And it can be brought on the Internet. Of course testosterone is used in male drive problems, and has probably been abused to a very great extent in men. Over the years testosterone has been perhaps the first line treatment for any sexual problem with the exception of premature ejaculation. I think doctors are probably a little more responsible now, and limit their prescribing of testosterone. But it is still being used in general practice as a first line treatment for impotence and yet we know that less than 5% of men with impotence actually have a testosterone deficiency. And studies have shown that if you give men with normal testosterone levels testosterone it doesn't actually their erectile activity.

Lets go back to the late 60s, early 1970s, you've talked about an issue to do with developing instruments. What kind of instruments did you have, and who was actually responsible for developing instruments
When I say instruments I'm talking about questionnaires. One of the big problems in this area, which is probably true in other behavioural areas as well, is that every person that wants to do a study starts by designing their own questionnaire without actually validating it

This has been a real problem over the years. I did a search a little while ago, and I think over 3000 different instruments for looking at erectile dysfunction had been designed or used over the years. Some of these are slight modifications of pre-existing ones. But it wasn't until pharmaceutical companies started to get interested in the area, particularly Pfizer, that there was money available to

develop questionnaires and validate them. This led to the international index of erectile function, on which I was the second author, which was the first well validated instrument for male sexual dysfunction. And since then there has been interest among pharmaceutical companies, mainly Pfizer again, looking at Viagra in women which had led to the development of questionnaires for female sexual dysfunction and these have been quite well validated now also.

So I think we are now at a stage of having some well validated instruments except for sexual drive. Although we've got some instruments that are supposed to be validated for sexual drive I think they are quite inadequate, and we need to look more at that. The other instruments of course apart from questionnaires are the more physiological instruments, where one can in men measure erectile function, and these have been used in therapeutic practice for years

Plethysmography?
Well that really only measures enlargement of the penis and of course in addition to enlargement rigidity is important and I think the major step for measuring rigidity was the Rigiscan. This is two rings that are put one round the base of the penis and one round the head of the penis and the rings are connected into a machine. At regular sampling intervals the rings tighten and as soon as they meet penile resistance they record, so they are measuring circumferential rigidity. This is not the most ideal measure. What one really wants is axial rigidity. Some axial rigiometers have been developed which are sort of pressure gauges that you put on the end and you read off when you press hard until the penis starts to buckle. This has been used in research in some centres but has never been really used in clinical practice. There hasn't been a need for it clinical practice.

The other thing about the Rigiscan is that one needs a stimulus, and there are two ways. One is to use erotic videos and the other way is to look at nocturnal tumescence. If one is looking for a drug treatment for erectile dysfunction, then erotic videos are the most important aspect.

On the female side vaginal blood flow measurements have been used probably since the late sixties or early seventies. This is much more difficult than penile plethysmography, but you can monitor vaginal blood flow and this equates with physiological arousal. The most effective way of doing this is not with photoplethysmography but is using radioactive clearance methods to look at vaginal blood flow. But there are very few centres that will do that actually. Most of that work has been done by Paul Vargner, in Copenhagen

The big problem about women and physiological measurements is that there is a very poor correlation between what happens in the vagina vis a vis blood flow changes and the women actually feels. And this is one of the problems that one is seeing when we are treating arousal dysfunction in women. We know that Viagra or phosphodiesterase 5 inhibitors are going to increase physiological

arousal and this has been shown. But in most of the studies where they have looked at this, women haven't appreciated any changes,

And of course its feelings that women want not necessarily changes in their vaginal haemodynamics. And I think this is one reason why this class of drugs may not be universally effective in women.

You mentioned Copenhagen. In the late sixties, early seventies was sexual medicine a different problem in the UK than it was in the US or in Europe. Were parts of Europe more open than we were etc or did it all actually appear to develop in these places at much the same time?
I can't recall what it was like in the 60s. We had the perception, whether its true or not, that America at that time was further advanced than we were in providing services for patients. But I think this reflected the system of medicine - there were a lot of counsellors, a lot of therapists in America. A lot of psychologists who were changing and becoming interested in sexual problems after Masters and Johnson had published their work in the mid 60s. This triggered interest in among the psychologists

I don't know what was happening in those days in other European countries except to say that in Holland I think they have been very much more progressive in providing training for doctors and psychologists in sexual medicine. Every medical school in Holland has a chair of either sexual medicine or human sexuality or something that relates to human sexual functioning. And that hasn't happened in the UK.

I think from the point of few of other European countries, there have been one of two people interested in this area, in other countries, like Paul Vargner in Copenhagen, and they were producing a lot of research papers at that time. The other person in the UK that was interested in sexual physiology was Roy Levine in Sheffield who has recently retired. He was reader of physiology in Sheffield, and he did a lot of work on vaginal lubrication, and vaginal blood flow. Often in combination with Paul Vargner - they published together.

It was their work initially that showed that sexual arousal was really not a cholinergic function. It had been thought in the 60s that sexual function was primarily cholinergic. Both their work and some I did subsequently showed that you could not inhibit sexual response in women by giving atropine. And I guess this is where we first started thinking in terms of other neurotransmitters being involved in sexual arousal.

It wasn't until the late 80s I think when nitric oxide was first discovered as a neurotransmitter and then in the early 90s as a fundamental neurotransmitter for sexual arousal. The other person who did some work in sexual arousal was Steven Bloom at the Hammersmith Hospital the Professor of endocrinology who was interested in peptides. He showed that during sexual arousal in both men

and women, there is an increase in VIP in blood flowing away from the genital areas. VIP, or vasoactive intestinal peptide, was subsequently used as an injection treatment for erectile dysfunction. It never got a license except for one product, which is a combination of phentolamine and VIP which got a license but has never been marketed.

This brings us on to PIPE treatment – Papaverine Induced Penile Erections. From the outside most people will wonder how could such an extraordinary have ever been discovered. How could someone for the first time, plunge a needle into their or someone else's penis to see what happened?
I think the first person that recognised the potential for local treatment for erectile dysfunction was Mikhel a vascular surgeon working in Prague. If my recollection is correct, he was using papaverine to dilate pelvic blood vessels during surgery and noticed that the men were getting erection when it spilled into the penile blood system. I think he wrote a letter about this actually, and soon after that a person called Virag working in Paris another vascular surgeon started to inject papaverine into the penis

Around about the same time Giles Brindley, a delightful man, who was professor of physiology at the Institute of Psychiatry, at the Maudsley Hospital, picked this up. My understanding from what he said at various medical meetings was that he had a prostatectomy and was rendered impotent. And he was always looking for treatments for his impotence. Reading Virag's work, he started to inject his own penis with papaverine, found it was effective. Then he used his own penis as a model for evaluating a whole range of drugs. His most interesting paper was in the Journal of Pharmacology where he describes about 10 different drugs being injected into his own penis and what each did.

I wasn't at the meeting, but I'm sure its true that at one medical meeting he dropped his trousers and injected his penis in front of the audience. I've heard this from so many different people that it must be true.

Brindley actually had a whole series of patients that he was seeing at the Maudsley, many of whom had spinal injuries and other neurological problems and he evaluated intra-cavernosal injection therapy in these patients.

This was the early eighties.
Yes. First of all papaverine was being used on its own. There are two problems with this. One is that some monkey studies showed it to be hepatotoxic though this was in massive doses. But it did scare people into not using it. The other problem was the unpredictableness of the drug. So people started looking for other drugs that could be given intra-cavernosally and phentolamine, the alpha blocking drug was being used, sometimes in combination with papavarin. And then Prostaglandin E, alprostadil, was found to be effective. All credit goes to Upjohn for this because they progressed alprostadil to the market and it became the first drug we had for sexual problems. And then there were searches

Was it actually the first drug bought onto the market for sexual problems
Yes it was, except for benperidol which was used for antisocial sexual behaviour and that had a license before, but there is no reason to think that that is any different to haloperidol

Its just they had another -idol hanging around the place and wanted a niche for it?
That's right

As regards PIPE treatment, the search then was really on to get a low incidence of pain during the injection and a predictable erection that was really dose related so that you knew that the man would get an erection and how long it would last. One of the problems with this class of drugs is you get an erection that doesn't go down again - you get priapism. So alprostadil fitted the bill but we were still seeing priapism.

People started experimenting using small amounts of alprostadil with small amounts of phentolamine and small amount of papaverine. That was known as Trimix. A lot of people still use that. Its not commercially available but they claim a very low incidence of priapism with that. Then VIP became available and people started experimenting in VIP. It's not very good on its own but when used in combination with phentolamine, it seems to be quite useful.

Phentolamine is an alpha blocking drug. There was another drug available at Fournier laboratories, a French company, which was a good alpha blocking drug that was traded as Erectos (?chemical name). And that drug was very good actually. It gave a predictable erection but the advantage over alprostadil was that it required sexual stimulation to have an effect. So it was a very good drug to use in combination with behaviour therapy where you could encourage people to have more sexual stimulation. This drug is still available in France and other European countries but for commercial reasons it was taken off the British market.

How did it work?
It's an alpha blocking drug working within the erectile tissue to relax the cavernous tissues.

Why should it only work with behavioural stimulation?
Because the vaso-dilatation within the penis requires nitric oxide release and you only get that in response to sexual stimulation,

To answer the point you were making about how men could inject their penises, I think the answer is that if that's the only treatment available and its effective then they will suffer the discomfort. But nevertheless even before Viagra, there was the thought that men didn't really want to inject their penises and companies

looked for alternative routes for administration. This led to trials looking at transdermal alprostadil and transdermal nitrate. Now one approach is to administer alprostadil through the urethra in little pellets in a treatment called MUSE. This seemed quite a good idea because it avoided a needle, but my experience was that a lot of men would prefer a needle to putting something down their urethra. And the overall the efficacy of transurethral alprostadil does not match the drug when injected intracavernosally.

There is on going work looking to see whether one can improve the efficacy of transurethrally administered drugs such as by adding an alpha blocking drug to alprostadil, but I don't think that any of these are near the market place at the present time.

When I'm giving patients intracavernosal injection if possible I teach the partner to do the injection. And a lot of women are very happy to inject their men's penises. But I've not found a woman who is willing to use MUSE on her partner. Women just do not want to put something down their partners urethra but they are willing to inject the penis and I think its important actually that partners are involved so because the woman can then own the erection. A very common comment we get back from women is that he doesn't need me for his erection he has his injection. It's not my erection it's his erection. So I always try and encourage the couple to do it jointly. Ideally for the partner to do the injection but if she is not willing to do that, than perhaps get the things out of the box so that she is involved in some way with it just to enable her to feel that she impart at least is responsible for that erection. But they wont do it with MUSE.

You worked in the industry through the 70s and 80s?
From 1976 for fourteen years. But I had my own practice as well and I had my own laboratory where we did our research. Glaxo at that time did not want me to do my sex studies on their premises so they set me up a laboratory in my home and I've still got all the equipment.

So this is an odd kind of arrangement. How did things get to the point where you were allowed to set up in your own home at an arms length from Glaxo?
What had happened in fact was that I did my training in general practice. I then went to Manchester to do a masters degree and I got appointed a lecturer there. But having just left general practice and a broken marriage I really couldn't afford to live on an academic salary, which back in those days was abysmal. So I looked around for a source of income in something that really interested me, and this led me to the Glaxo group, or as they were then Allen and Hanbury's.

I told them what I wanted to do, and they gave me a job. It was a full time job, but I said wanted to continue my practice in sexual medicine and also research and they said basically that I could have time to do my practice and then when I started researching they didn't actually say we don't want it on the premises but

they did give me the facilities to do it elsewhere. And we had a large house that lent itself to setting up a laboratory there.

What was in the lab?
Well I had photo-plethysmography. I had centrifuges. I had reagents and that's all I needed really.

And at the time, the things you worked on were these linked up to clinical trials?
They weren't linked up to clinical trials but I used some Glaxo products. One of our studies was a premature ejaculation study, using tryptophen DA, which is a perphenazine neuroleptic and amitriptyline. This in fact was the first placebo controlled premature ejaculation study that was published and it's the only study published to date where anyone has compared active drug treatment with squeeze techniques. Pharmacological with behavioural. We showed that at the end of 12 weeks there was no difference between the two groups but the group of patients that had squeeze technique plus pharmacological treatment gained ejaculatory control much sooner, than the group that just had behavioural therapy.

We also looked at the effect of labetalol, both an alpha and beta blocking drug on female and male sexual responses. We showed that labetalol delayed the loss of erection after penile vibration. And we showed that propranolol didn't do that. Now the only difference between propranolol and labetalol was the alpha blocking component of labetalol and therefore we were probably the first to show that alpha blocking drugs actually delayed the loss of erection, which pointed to a potential in the treatment of erectile dysfunction. And we looked at labetalol also in women, who showed a delayed orgasm on it.

Where did you get the volunteers for these studies?
We had no shortage of volunteers actually. We still do volunteer studies - secretaries or nurses. It was very difficult to get male volunteers but females in those days were very willing to be involved.

Why would men not do it and women would?
Well we did studies in men, but women just seemed to be more enthusiastic about taking part in studies, probably because in most drug trial studies women are excluded, because of the inconsistencies in their responses during the menstrual cycle. So here were studies designed for women and they were very keen to participate. I don't think it was necessarily because they wanted to be involved in sexual things. I think it was because they wanted to be involved in research. A lot of these early volunteers in fact were people working within the industry.

Somewhere around the mid-1980s, the companies put a block on company employees getting involved in healthy volunteer work because of the perceived element of coercion.
Yes, I think what happened was this. But thinking about Glaxo now they still have a large clinical pharmacology unit and use their own employees.

But certainly in the mid-80s, there was a revision of volunteer studies because there was a death in a unit in Cardiff and then a death in one of the pharmacology units in London and the Royal College of Physicians got involved. But despite this we don't find any difficulty in generating work here.

The other issues which goes parallel with this that you have hinted at is that in the 60s you'd have used slides that wouldn't cause people to bat and eye now but I guess now you are almost into online sex?
Well I mean one uses videos but this is one of the problems with this type of study. Its very difficult to find a video sequence that will turn all your volunteers on. Some people get round this by letting volunteers choose their own video sequence but the problem then is that this reduces the standardisation

The other issue of course is that in most studies that one needs multiple challenges. Does one use the same video sequence for each challenge or does habituation occur or should you use a novel sequence each time. But if its a novel sequence, perhaps one is more erotogenic than the previous one, which would upset the study. We believe actually that responses to erotic videos are probably more or less constant over four different exposures of the same images. So you can do a four way cross over perhaps but not any more than that.

But it really is interesting how people's responses to erotica have changed over the years. Looking back to some of the slides we used to use, you see the same pictures in the daily papers now.

So in the mid 1970s you were working with Glaxo. What happened next?
I worked in the Glaxo group until the late 80s but I still had consultancies with various pharmaceutical companies. On of these was with Syntex where I helped them develop Delequamine. This work involved a lot of travel. They were very exciting times because I was able to travel the world talking to various experts. It was the first time companies really were setting up large scale studies in erectile dysfunction. This was around 1990.

With Syntex I was under contract to run their clinical trial programme, both from writing the protocol but also going out to setting studies up in various centres. And it enabled me to go off to America to meet what were mainly urologists in America but also to Canada and most European countries

Who were the key people around the place?
Key people at that time in America included Irvine Goldstein, who was really fundamental. Jo Lopiccolo, a psychologist, Taylor Seagraves, Ray Rosen, some people in California like Tom Lew, Moralis in Kingston, Richard Kayson and Colin Shapiro in Toronto.

You say the people over in North America were mainly urologists
They were essentially urologists, yes. Sex therapists as such were much more behavioural therapists. In those days urologists were the treaters of erectile dysfunction Most people with erectile dysfunction went to a urologist. And we were also looking for people with Rigiscans to proper physiological measurements on people and it was the urology clinics that had the facilities to do these studies.

What was the mood or the atmosphere meeting these people? Did you guys feel you were making a new field at that stage?
Yes. I mean the majority of investigators were enthusiastic. A few were thinking that perhaps a centrally acting drug may not be the right way to go for treating erectile dysfunction. Some of these people at that time were having other ideas about treating erectile dysfunction. But we were met with a lot of enthusiasm and we were getting people writing to the company wanting to be investigators, because as I say it was really the first large scale multi-centred study.

This was pre Viagra?
Yes a long time pre-Viagra. I had finished with Syntex before I started working with Pfizer. I can't remember the dates exactly, but it was certainly a very exciting time both for myself and the investigators. I was seeing something coming to fruition that I had thought about throughout my medical career - that we should have specific drugs for sexual problems

Now when Pfizer actually approached you about Viagra, what was the overture like? Did they say we've accidentally discovered this has sexual effects can you help us explore it or what?
Um yes they asked me to advise them on protocol design initially. I didn't myself take part in any studies at that time

Can you remember any sense of surprise that Viagra did what it did, or not given that had been some suggestion for years that nitrites were aphrodisiac
That's right yes. The nitrites were known to have some effect on orgasm. I'd already read some of the work that had been done on nitric oxide and sexual arousal in animals at that time - some of Tom Lews work. So really before Pfizer came to me, I was au fais with the idea that nitrites were involved in erectile function. And the pharmacological properties of Viagra seemed to fit the bill in that respect. The one thing that surprised me more than anything else actually,

something I was really quite uncertain about in the beginning, was the selectivity of the compound.

I still find it quite hard to believe actually that phosphodiesterase-5 is concentrated in the erectile tissue

Yes it is fairly odd, given that most of the things that are in the brain are in the gut and everywhere else as well.
That's right. I think phosphodiesterase-5 has now been found in the brain, and I suppose that raises the possibility as to whether Viagra actually has a central as well as a peripheral effect. But, I was quite excited about it.

Was it clear from the start that the drug really worked - did it require much clinical trial protocol development or was it just a case of putting the minimum in place where it really obviously works?
Well the first published study was a volunteer study by Clive Gingal, a urologist in Bristol, who showed that Viagra enhanced erectile responses to erotic videos, and it was really quite reassuring in fact that this was a viable target. And then when the clinical trials were done it was so obvious, on even quite a small number of patients that it was working. I think there is no doubt at all that the discovery of phosphodiesterase-5 inhibitors was a major advance in the treatment of erectile dysfunction. They provided effective treatment by a route which was much kinder than sticking a needle in the penis.

In the case of Viagra the company talks about it openly as a lifestyle agent, but on the opposite extreme you have the Minister for Health in the UK saying well we are not going to let it be prescribed on the NHS other than if you've got some medical conditions and they've excluded quite a lot of medical conditions. Can you take me through this?
Yes well there is no doubt at all that erectile dysfunction has a devastating effect on the sufferer and often on his partner as well. Therefore if one wants to improve their quality of life, their erectile dysfunction needs treating. I personally don't like the word lifestyle drug for any treatment of erectile dysfunction because I think we are actually treated what is potentially a serious problem. People have committed suicide.

But is it aphrodisiac over and above its therapeutic effects in ED?
No, there is no evidence at all that Viagra or any of these treatments actually increases people's sexual drive. This may be a reflection of poor assessment instruments, but the data that's available shows that these drugs restore erectile function and that men are not having intercourse anymore frequently than a control group of people that didn't have erectile dysfunction and were not using Viagra. So it's restoring their sexual function to whatever the norm is for that age group. I do not believe that these drugs can be classified as aphrodisiac even if they do increase sexual drive to a small extent - it can't be to a large extent because that would have shown up.

I don't like the word aphrodisiac. Its difficult to define just what it is actually. To my way of thinking, an aphrodisiac is something that actually increases sexual drive above and beyond the norm, and we haven't got a drug at the moment that does that not even testosterone

The other part of your question of course is limitation put on the use of these drugs and this is purely a financial consideration. I think it's appalling that people can have their treatment if they have one condition but not if they've got another condition. Diabetics are allowed treatment on the health service. You don't have to confirm that their erectile dysfunction is due to their diabetes. It could well be due to behavioural or psychiatric problems but they are still entitled to free treatment. Whereas people with cardiovascular disease are excluded, and we know that cardiovascular disease is a major cause for erectile dysfunction.

It's quite an irrational list that was politically generated. And we don't know who actually told the minister what conditions to put on this list. One of the conditions is a single gene abnormality leading to a neuro-degenerative disease, which I had never heard of at the time, so I am fairly certain the Minister of Health didn't know what it was. I sat on one of the committees that was advising on this and they didn't actually take advice from that committee at all.

Viagra has also opened the issue of going round the back door and getting your supplies through the Internet?
Yes. its caused a lot of medical practitioners to prostitute their position in that they have been either selling drugs on the internet or setting themselves up as specialists in ED, notionally to provide treatment for men with ED, but I think their motivating factor is financial reward for this and as you say I mean some doctors have been selling the drug on the Internet which I think is malpractice

But it's a safe drug?
Its very safe providing the person isn't taking nitrates when it can be potentially fatal. But erectile dysfunction is not a disease it's a symptom, so that just by giving a man Viagra you may well solve his problems but his diabetes might be getting worse. Every man that has erectile dysfunction should really see a doctor or health care professional to be screened for diabetes, hypertension, high cholesterol and all the other potentially serious medical conditions of which erectile dysfunction will be a symptom.

Has Viagra made the field of sexual medicine respectable?
I'm not sure that sexual medicine as a specialty has become respectable because there still isn't a career structure, and there are still many hospitals that will not set up sexual medicine clinics. Most hospitals provide services in sexual medicine via the GUM clinics or AIDS clinics on money which isn't really meant for sexual problems but is meant for the treatment of infections and may well stop in the future. The clinic I ran at St Georges was a very active clinic and we were

making a lot of money for the Hospital, but when I left St Georges they used my departure as an excuse to close the clinic. And I am aware of other trusts that have closed down their sex therapy clinics

What's the thinking?
I think the thinking purely is economical, and that sex is still an outcast to some extent. The government has talked about investment in cardiac disease and cancer, but it never mentions sex, even though the World Health Organisation says that every person should have the right to a happy sex life

I think the other issue is one of training. I'm essentially self-taught over the years. When I started there weren't any training programmes and there still aren't really. One group of doctors who are very well trained are from the Institute of Psychosexual Medicine, but their philosophy over the years has been very much oriented to counselling and psychotherapy and until very recently they resented or resisted any physical treatments at all

There is no other recognised training programme. We run a Masters course in Preston in sexual medicine but we can't run it this year, although we've had a lot of applicants. None of the applicants has got funding to do it - their trust has denied the funding, which is unfortunate. I would like to see one of the Royal Colleges forming a sort of faculty of sexual medicine. Discussions were held in the past with the College Of Psychiatrists, John Kennet, but they seemed quite reluctant to take this on. We used to have a training programme at Queen Charlotte's hospital which I used to teach, which gave a diploma in sexual medicine, but that was closed down for political reasons - they didn't want to have a sexual course there.

People like Hannah Steinberg in the 60s were doing work on rats and other animals with compounds that sexualised the animals but these didn't get developed. Roland Kuhn in his first clinical trials for Geigy with a range of anti-histamines reported that some of these actually eroticised women, but again these didn't get developed, how much do you think there is sitting on shelves which companies suspect have these kind of effects but haven't ever developed and could any of these things be working by quite different means to the drugs that we know do have an effect?
That's a difficult set of questions. I am convinced that there are compounds available that have not yet been evaluated and probably will never be evaluated, that would have the potential for altering human sexual response. We know that for instance that there are many dopamine agonists available because they are supplied for animal studies.

Sigma is one of the companies that produce a lot of laboratory reagents and you just need to look down their index to see all the dopamine agonists that are available. So yes, there are compounds on shelves that would have the potential

for changing sexual functioning. In both directions – both increasing and inhibiting.

Whether they work by different mechanisms, I wouldn't like to say. I think we know very little about the central mechanisms of sexual functioning at the moment. We know that dopamine is important; we know that noradrenaline is important centrally. We know that 5HT-2 and that certain neuropeptides are involved and there is some interest in looking at neuropeptides at the moment. But we don't really know very much else about human sexual functioning.

Whether one can use animals as a model for human sexual functioning, I'm not sure. I mean you can use models for erectile activity, but I'm not sure whether one can use models for sexual drive and sexual desire. I separate drive from desire, as two different functions. I think human sexuality has evolved to such extent that a lot of our primary sexual drive mechanisms are probably modified by higher centres in a way that does not apply with animals.

I think we may well see that drugs will enhance sexual activity in animals but will have no effect in humans. I really don't know what mechanisms are still to come. I think the increasing use of functional MRI is really quite important because at the present time we know so little about what centres are involved in the brain for controlling sex. We know that the preoptic area and paraventricular nuclei are important and parts of the limbic system. But its really quite gross what we know, and I hope that functional MRI may be one way that we can identify what parts of the brain are involved.

These are very expensive studies, until this technology becomes much cheaper. But most of the advances in our understanding of sexual functioning has really come from pharmaceutical company funding. So although Masters and Johnson and one or two other people back in the 60s described the morphological changes that occur in sexual responses, it really wasn't until pharmaceutical companies got interested in this area that there was money to dissect out human sexual response in more detail and there is still a long way to go.

Let me take you to another theme. When Kuhn wrote his first paper on Imipramine, he outlined the case of a man who was homosexual, who on imipramine normalised apparently. Then Peter Kramer in his book Listening to Prozac described a very similar transformation of a guy who had a paraphilia of some sort. Anecdotally there are stories of various different psychotropic drugs being given to people with paraphilias and people changing fairly dramatically. There's no great reason to think this hasn't happened. But there isn't any great reason either to think that the thing couldn't happen the other way round, with normal people becoming paraphiliac or whatever - which you wouldn't hear about. This is not sexual functioning as such.

No, it's an area I don't know very much about. There is no doubt at all that the SSRIs can be effective in a group of patients with paraphilias. There has been one or two not true studies but quite large series of patients but they weren't homosexuals. Paraphilia and homosexuality are probably two very distinct conditions. I think homosexuality is a variant of normal with a biological basis rather than a psychiatric basis. Paraphilias on the other hand I put more into the class of mental disease.

Nothing I've read or seen would make me think that these drugs could induce homosexuality. I would find it extremely difficult to understand that. Perhaps they could make a latent homosexual more confident and make him able to come out and express his homosexuality. From the paraphilia point of view, I don't know to be honest, I don't know enough about the aetiology or psychophysiology of paraphilias to comment on it

I try not to be involved in paraphilias too much, although last year I got the gold medal of the Royal Society of Medicine for a lecture I gave on the sources and development of sexual identity. But I knew nothing at all about it before I had to produce that lecture. My understanding of paraphilias and sexual identity is really quite new

Finally, is the area of female sexuality still something of a mystery?
Yes. It's lagging behind the male area by a very great extent. I don't honestly think that we will find a drug for use in women, which gives the same benefit as Viagra does in men. I think female sexuality is so tied up with emotions and central mechanisms that even if we can increase her physiological arousal by an enormous amount it may not satisfy her needs. She wants the feely things, the emotional involvement and drugs aren't going to do that. And I do believe that in women its even more that we should combine drugs and behaviour therapy.

So on that line of when you get the reaction from an audience who do not want sex medicalised, do you find that it's the women more than the men who react that way?
It tends to be the therapist whether they are male or female. Actually it tends to be the non-medically qualified therapists but the women would be more inclined to say look sex is not a mechanical thing and you are treating it as a very mechanical thing.