

Female sexual dysfunction: some research issues

by

Dr Steven J. Fisher, Department of Molecular Biology, University of Oxford.

International Journal of Sexual Biology 2008 May; 29(3):701-50

ABSTRACT

BACKGROUND: Male sexual dysfunction has been well described in the literature. The compound sildenafil citrate, marketed by Pfizer under the brand name Viagra, has created a market estimated at over \$1billion annually. This has led to speculation that a drug targeted at female sexual dysfunction or FSD will be “the big pharmaceuticals’ next miracle cure” (Newsnight, June 2007). However, the existence of FSD, and therefore of a treatment to combat it, remains controversial.

METHOD: The author describes a project to investigate a possible treatment for FSD, and cautions that some previously unconsidered factors may affect clinical outcomes. He describes in particular the case of Miss G, a research subject.

DISCUSSION: This paper was first presented at the conference “Towards a Sexual-Dysfunction-Free Future 2008”, sponsored by Trock Pharmaceuticals, where it provoked a lively response (see, for example, the correspondence pages of this journal, *passim*).

INTERESTS: The author acknowledges the generous funding of the Trock Pharmaceuticals Research Foundation. This funding has since been withdrawn.

1.1

Twenty-eight women have now participated in the sexual dysfunction research project here at the Department of Molecular Biology, Oxford University. Our approach is empirical: that is to say, the treatment, a synthetic enzyme codenamed KXC79, is adjusted in response to each set of results. All the participants are volunteers and are assessed by my colleague Dr Susan Minstock using a number of standard evaluations (the Derogatis Sexual Functioning Inventory, the Locke-Wallace Marital Adjustment Test, the Female Sexual Function Index, etc) before a decision is made as to whether they are suitable for inclusion. It is always explained to the volunteers exactly what the study will involve; to date, thirty-one potential subjects have subsequently declined to take part. Nevertheless, early results have been encouraging (see, for example, Fisher, S.J and Minstock, S, 2007: *KXC79 and female sexual dysfunction: some encouraging early results*).

Miss G was slightly unusual in that she was a postgraduate student here at the university who heard about the project from one of our research assistants.¹ Strictly speaking, this was a breach of our selection protocol. However, Miss G worked in a completely different field, English Literature, and in all other respects fulfilled our criteria: she was anorgasmic and had previously consulted a doctor “to make sure it wasn’t just a virus.” (Notes were kept from initial and subsequent interviews: in addition, like all our volunteers, Miss G was encouraged to keep a record of her subjective responses during the trial.) She had also experienced relationship problems:

It wasn’t just that I couldn’t have orgasms – it was the fact that sex was such a big part of his life, and I couldn’t share that. I simply had no interest in it. Almost as if I were going out with a football fan but was bored by sport.

Based on this discussion and the questionnaires, Dr Minstock made a provisional diagnosis of Hypoactive Arousal Disorder and accepted her onto the study.

¹ The research assistant has since been terminated.

I myself met Miss G for the first time when she came to the lab for her induction. As this meeting, apparently so ordinary, was in some ways the beginning of the whole fiasco, I suppose I should at this point pause to note my initial impressions of her – as a person, I mean. The truth, though, is that I did not really have any. If I may be allowed a small subjective observation of my own, what I recall most is being somewhat annoyed she was there at all: my understanding was that the data-collection phase of our study was completed, at least for the time being, while I prepared our findings for publication. This was work that required a great deal of concentration, and when Dr Minstock showed someone into the lab I did not, at first, look up from my computer.

“This is where the hands-on part happens,” my colleague was saying. “When I say hands-on, of course, I don’t necessarily mean that literally. We’ve got toys to suit every taste.”

Needless to say, I did not respond to this, either. Dr Minstock’s jocular manner, which she frequently assures me is simply a psychological stratagem to put test subjects and co-workers at their ease, on occasion strays – it seems to me – into flippancy. Great scientists of the past – men such as James Watson and Francis Crick, when they were engaged in their revolutionary work on DNA – felt no need to be flippant. But Dr Minstock, as a sexologist, does not have quite the same regard for scientific method that I do.

“That’s Dr Fisher, who’s in charge of the biochemical side,” she added in a deafening whisper. “Working away, as usual! Don’t worry, we won’t disturb him if we’re quiet. Over here’s the photoplethograph – basically it’s like a little light so we can see what’s going on –”

“Photoplethysmograph,” I said, still without raising my head.

“What?”

“That is a photoplethysmograph, not a photoplethograph. It calibrates reflected light. The darker the flush, the greater the vasodilation.”

“Oh, yes,” Dr Minstock said brightly. “Photoplethysmograph. Of course.”

“What’s ‘vasodilation’?”

I did look up then. There was something about the voice that had just spoken – something wry, ironic even; as if the speaker were somehow mocking herself for not knowing the answer.

Or – it occurred to me a fraction of a second later – as if she were somehow mocking *me* for knowing it.

In short, I thought I had discerned in the way our visitor had spoken a spark of natural intelligence, an impression only partially dispelled by her appearance. I did not at that point know Miss G was an arts graduate, but I could probably have deduced it. She was attractive; strikingly so – I might as well make that clear at the outset. But she was striking, if this makes sense, in an entirely unremarkable way. A pleasant face, torn jeans, a cashmere pullover, a book bag, a knitted cap; and, spilling out from under the cap, a fine mass of chestnut-brown hair, as squeaky-clean and glossy as a freshly-peeled conker. One could imagine that if one were to touch it, the hair would be expensive and soft, just like the pullover. Clearly, she was not part of the university I inhabit, bounded as it is by the Rutherford Laboratories on one side and the Science Parks on the other. Hers was another Oxford entirely, a city of drama societies and college balls and open-top sports cars roaring off for candlelit meals in country pubs. In that Oxford, which overlaps mine while barely impinging upon it, girls like her are... I almost want to say ‘two-a-penny’, but of course they are considerably more expensive than that; their cashmere pullovers, their poise, and even their places at Oxford are the products of costly private educations.

So I glanced at Miss G and immediately thought that I knew her type; a type which was both as familiar and as alien to me as if she were a member of another species.

In this, as it later turned out, I was quite wrong.

“Vasodilation,” I said, “relates to blood flow. Specifically, engorgement of the surface capillaries due to physiological stimulation.”

“Anything you want to know about the technical stuff, Steve’s your man,” Dr Minstock said, with a little roll of the eyes which clearly suggested that knowing about the technical stuff was a long way down her own list of priorities.

“Actually,” Miss G said, “There was something.”

“I just need to check that file,” my colleague said quickly. “Back in five.” As she left it seemed to me that she gave the other woman a pitying look, as if to say ‘I warned you’.

I sighed as I turned back to our visitor. “Yes? What did you want to know?”

“This treatment of yours,” Miss G said hesitantly. “It’s something like Viagra, presumably?”

I regret to say that even before she had finished this question I was smiling slightly at its naiveté. “Not in the least, no. Viagra would be completely the wrong approach for any problem you might have.”

“Why’s that?”

“Well, I can tell you if you like,” I said. “But I very much doubt you’ll be able to grasp the answer.”

She looked at me then in a rather level way, and I thought I detected a slight tightening of her jaw.

“Dr Fisher,” she said carefully, “I have a double first class honours degree from Bristol University, an MPhil from Cambridge, and I’m three-quarters of the way to completing a PhD here at Oxford. How about you try me?”

1.2

My explanation will undoubtedly seem rather simplistic to my present audience, but for the sake of establishing exactly what I said to Miss G, I will repeat it here. “The active ingredient in sildenafil citrate, or Viagra, is a specific inhibitor of phosphodiesterase 5,” I pointed out. “This cleaves the ring form of cyclic GMP, a cellular messenger very similar to cAMP. The inhibition of the phosphodiesterase thus allows for the persistence of cGMP, which in turn promotes the release of nitric oxide into the corpus cavernosa of the penis.”

She nodded slowly. “You’re quite right.”

“Of course. The mechanism is relatively well understood.” I turned back to my computer screen.

“No, I meant you’re right that I didn’t understand. Not a word. Mind you,” she went on, almost to herself, “it’s got a sort of music to it, hasn’t it, and I don’t always understand a piece of Tennyson or Keats when I first hear it, either. Sometimes you have to sort of... *feel* the meaning before you can work out the details, don’t you? So let’s see... what you’re saying is that once the phospho thingy, the phosphodiesterase, is taken out of the equation, and the cyclic GMP does its stuff, it’s basically a question of nitric oxide, which must be a gas. So really it’s just about hydraulics.”

I must admit, I was quite intrigued that she had managed to work out the gist of what I was saying from so little actual knowledge. But that, I suppose, is one of the differences between science and the arts – they are positively encouraged to speculate

beyond the realms of what they know, whereas for us, of course, it would be anathema. “Approximately, yes,” I said. “Women’s sexual responses are rather more complicated.”

“Ah. Now there, perhaps, I can correct *you*. You mean ‘complex’.”

I frowned. “It’s the same thing, surely.”

She shook her head. “‘Complicated’ means something difficult but ultimately knowable. ‘Complex’ implies something with so many variables and unknowns it can only be appreciated intuitively. Like poetry or literature or love.” And then, somewhat to my surprise, she recited what I took to be some lines of verse.

“When two are stripped, long ere the course begin
We wish that one should lose, the other win.
And one especially do we affect
Of two gold ingots, like in each respect:

The reason, no man knows. Let it suffice,
What we behold is censured by our eyes.
Where both deliberate, the love is slight.
Who ever loved, that loved not at first sight?”

“Marlowe, Christopher,” she added. “1564 to 1593.”

“Then I stand corrected,” I said. “But even so, I still think I mean ‘complicated.’”

And then she asked the question that started the landslide.

“Oh? Why?”

1.3

I rarely get the opportunity to talk about my work. Because of the various irrational taboos surrounding the physiology of sexual response, and the even greater taboo surrounding scientific discourse, I find that when I try to explain to people what I do, either their eyes glaze over or they become embarrassed. So when someone asks me a straightforward question I take the view that the more I can dispel their ignorance with a straightforward answer, the better.

“What you call love,” I said, “by which I assume you actually mean romantic attraction, is a relatively simple phenomenon – cascades of a chemical called phenyl ethylamine gush through the central nervous system, inducing various emotional responses ranging from anxiety to a heightened need for touch. We know what it is, we know how it works, and, crucially, we know what it’s *for*. Evolutionary theory, Miss G, teaches us that everything in the human body has a purpose. Our feet are shaped the way they are so that we can walk upright on the grassy savannah. Our thumbs work the way they do so that we can shape simple tools. Our hair is sleek and soft and glossy so that our sweat glands can work effectively. The male orgasm is another case in point. It has one purpose, and one purpose only: the continuation of the human race. Any pleasure we feel is simply the bribe by which nature induces us to spread our genes more widely.

“If you hook a man up to a scanner during climax, you see a localised, muscular spasm lasting about six seconds: highly functional, but with little variation. A woman, on the other hand, gets pulled into it gradually, building up her orgasm in a series of waves.” At this point, I believe, I crossed to a whiteboard and sketched a brief illustration of the process, something along the lines of figures 1 and 2.

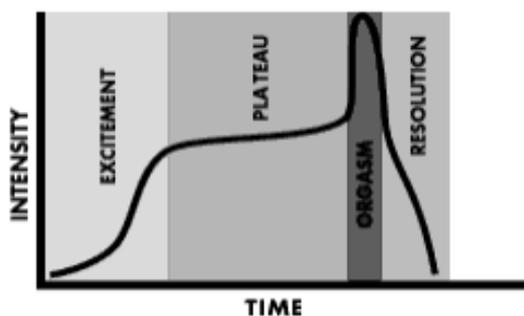


Figure 1: Typical male response

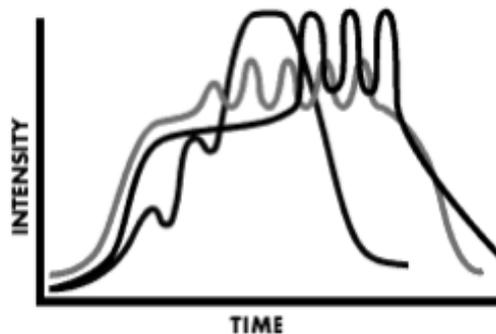


Figure 2: Three different female responses

“First comes the excitement stage,” I explained. “*Here*. There’s a reddening of your face, chest and neck, akin to a measles rash. A feeling of warmth pervades your pelvis. Your genitals engorge with blood; your pulse races, your limbs relax, you find it difficult to keep your mouth closed or control the sounds you make. A cocktail of stimulants, including dopamine and serotonin, are flooding your bloodstream,

sensitising your nerve endings and giving you a rushing sensation. Round about *here*,” I indicated with my dry marker, “your breathing becomes fast and shallow. Your capillaries dilate further, flushing your skin, which simultaneously becomes damp with perspiration. You are now at the stage scientists call ‘the plateau’, in which you feel as if you are being swept along on a rushing current of sensations. Synapses start firing in the right-hand side of your brain, the creative side, creating a flickering storm of electrical activity. Your nipples swell like berries. *Here* a chemical called oxytocin gushes from your pituitary gland, inducing an overwhelming feeling of euphoria. You gasp, you bite your lover’s neck, you shudder uncontrollably and your lips contort.

“Yet all this has just been the curtain raiser for the main event. *Here* your whole body stiffens. You have reached the point of no return, a feeling sometimes described as like being suspended at the top of a very high swing. You take a gulp of air and hold your breath, or grab your ankles and bellow. A pronounced frown – the so-called ‘orgasm face’ – is a testament to the myotonic tension now building in your muscles.”

I glanced at Miss G’s face. She was frowning with concentration as she tried to follow what I was saying, but I could see that she was more or less keeping up, so I continued, “At around this point, *here*, the long tissues of the arms and legs also contract in involuntary spasms. A shower of electrical signals twangs up and down the vagus nerve, like vibrations bouncing along a tightrope. A fiendishly intricate chain of biochemical reactions, only recently understood by science,² lights up your brain like a switchboard. The central nervous system goes into overload; patterns dance behind your eyes; you feel yourself propelled, judderingly, as if travelling fast over rough ground in a flimsy vehicle.

“But only now, *here*, do you finally abandon yourself to what is happening. A cascade of muscular contractions, each one exactly 0.8 seconds long, pulses outward from your genitals, until there is no part of you, from the centre of your hips to the tips of your fingers, that isn’t dancing to the same primeval beat. And then at last, *here*, it lets you go, although you may find after-shocks occurring up to half an hour later. For around thirty seconds, Miss G – perhaps for as long as three whole minutes – you have

² Fisher, S J: *Neurotransmitter cascades during climax of human females*, NuMed Chem III, 2006.

been in the grip of a sensation more intense, more extraordinary, than any male has ever felt.”³

There was a brief silence. It occurred to me that the use of the word ‘you’ might not be strictly accurate in this instance, since Miss G would presumably not have been in our laboratory in the first place unless she was having difficulty with some or all of this process.

“That is the how,” I continued. “But the interesting question, the question which has perplexed scientists ever since we started looking at this area, is the one you asked just now.”

““Why?””

“Exactly. *What is it all for?* The clitoris appears to be the only organ in the body which has no function other than pleasure; the female orgasm is the only physiological mechanism for which we can find no evolutionary purpose. It isn’t necessary for conception; it isn’t needed for eating, or sleeping, or raising young; it confers no advantage that can be passed on to the next generation. According to all the principles of natural selection, it shouldn’t exist. But it does. And – even more fascinatingly – it sometimes goes wrong, for reasons we still can’t entirely fathom either.

“That is the great mystery – and the great prize. In an age when we know almost everything there is to know about almost everything, the female orgasm is one of the few remaining puzzles. Your genitalia, Miss G, are the final frontier of scientific knowledge, the last great unexplored territory. Indeed, I would go so far as to say that scientists know more about the woolly mammoth than we do about your climaxes – and the woolly mammoth is extinct! But that’s changing now. Little by little, the bright light of research is illuminating the dark recesses of ignorance, and soon there will be no problem or glitch caused by Nature for which Science does not have an opposite and equal solution.”

I stopped, aware that I had spoken at rather greater length, and possibly with rather more passion, than I had intended to.

³ I should probably clarify that I was referring here only to the male and female of our own species. Amongst other mammals, the picture is more complex. Coitus between mink lasts approximately eight hours, though it is unclear how much of that is taken up by orgasm, as mink are notoriously irritable when sexually aroused and prone to biting researchers. However, it is known that a pig’s orgasm lasts around thirty minutes, while the orgasms of the female bonobo monkey are so frequent, and of such duration, that two or more can sometimes overlap. Fisher, S.J: *Multiple orgasm amongst the higher primates*. Journal of Endocrinology 74 June 2002: 91-121

“Goodness,” Miss G said, and once again I had the feeling that she might be mocking me, just a little. “You make it sound so much fun, as well. So, when do I start?”