

## LOVE SCIENCE

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There are times when science is just a lucky break; stumbling across something just by accident and then making something of it. For the science of love, it is the vole. Voles are small rodents of the genus *Microtus*.<sup>1</sup> They are often called “field mice,” but though they are members of the mouse family, they are not mice. They are voles. For our purposes, two particular voles are interesting. The first is the prairie vole (*M ochrogaster*), who happens to be monogamous. The other is the meadow vole (*M pennsylvanicus*), who is promiscuous. Because the two species are similar in just about every other way, scientists leapt at what is called an “experiment of Nature,” believing they had a key to the biological basis for monogamy and promiscuity.<sup>2</sup> And so they may.



PRAIRIE VOLE, MONOGAMOUS



MEADOW VOLE, PROMISCUOUS

Voles are vegetarian, so they can be pesky to have around the garden. Mostly, though, they are harmless. They breed frequently and reach sexual maturity at about 37 days. They tend to have large litters, which is a good thing, because they don't live very long. They are a major food source for owls, foxes, weasels, etc.<sup>3</sup> The prairie vole lives in the Great Plains and the meadow vole lives just about everywhere in the continental USA and Canada. The two species of voles have similar patterns of circadian activity, exploratory behavior, digging and nest-building. They are both highly social. The only difference between the two has to do with what biologists call “affiliative behavior.” The prairie vole mates for life, and is quite content to help his one-and-only raise the brood, or broods, since a loving pair have a new one every month or so. He lives in burrows with his extended family. The meadow vole, on the other hand, lives alone. Unencumbered by wife, babes or in-laws, he is the most prolific of all

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<sup>1</sup> *Microtus* means “small ear” and voles, in contrast to mice, have ears that barely protrude from the fur surrounding them. Greek: *mikros* (small) and *otos* (ear).

<sup>2</sup> Kimberly A. Young, Yan Liu, and Zuoxin Wang. The neurobiology of social attachment: A comparative approach to behavioral, neuroanatomical, and neurochemical studies. *Comp Biochem Physiol C Toxicol Pharmacol*. 2008 November; 148(4): 401–410.

<sup>3</sup> The mice that Farley Mowat ate whole ([Never Cry Wolf](#)) when he was living among wolves in the Yukon were probably meadow voles.

mammals and will mate with any estrous female who happens by. His paternal investment is zero, and he has nothing to do with his extended family, either.<sup>4</sup>

The monogamous prairie vole, in contrast, is paternally invested. Males and female prairie voles form long-term pair bonds, build a nest and take care of their offspring together. They are also aggressive towards any new vole that happens by. Their little “pups” (in contrast to meadow vole pups) show an intense stress response if they are separated from their moms or dads, make a lot of noise and secrete increased levels of stress hormones. All of this indicates, to biologists at least, that the prairie vole has something that the meadow vole hasn’t got, and whatever it is, it must be a *good thing* (Winslow, Hastings, Carter, Harbaugh, & Insel, 1993) (Shapiro & Insel, 1990)

After a good deal of scraping about, scientists narrowed the search to a couple of small molecules of the “neuropeptides” class. Neuropeptides are generated in the brain and behave a bit like neurotransmitters. They may also travel out into the rest of the body (“the periphery” to neuroscientists) where they behave like endocrine hormones. The two important neuropeptides are oxytocin, that is Pitocin®, the “pit drip” that is used to induce labor, and vasopressin, Pitressin®, which is used for a number of medical conditions, most commonly *diabetes insipidus* and *enuresis nocturna* in children.

We share oxytocin and vasopressin with the vole, and with every other vertebrate, and in all of us, the two peptides do just about the same things. So, before we get back to what makes some voles monogamous and others promiscuous, it is time for a pleasant digression.

## OXYTOCIN

Oxytocin holds the leading position among many candidates for the substance of “happiness.” If not “happiness,” at least it seems to be an important brain compound for building trust, which is necessary for emotional relationships and social bonds to develop. Scientists at the National Institutes of Health call it “the great facilitator of life” and they ought to know. The brain releases oxytocin (from the posterior pituitary gland) during childbirth, lactation, and orgasm, major events in the lives of animals and humans as well.<sup>5</sup>

Oxytocin and vasopressin are small molecules, made of nine amino acids (hence, “peptides”), and closely related to one another; in ancient times, they were one and the same. Very early in evolution, some kind of mutation occurred that gave rise to two separate peptides. They are still very close, although they have taken different paths, differing in only one of their nine amino acids,. The oxytocin lineage contributes to female social and sexual behavior in fish, birds, amphibians and mammals. The vasopressin lineage regulates male social and sexual behavior in all of the above.

Consider the toadfish (pictured), a vocal fish for whom grunts, boops and whistles are part of the reproductive repertoire. According to Goodson and Bates (2000), toadfish vasopressin regulates grunts in males while oxytocin (or the toadfish’s version thereof) regulates grunting in females. (cf, Can fish hear?, Chapter \_\_).

<sup>4</sup> When prairie voles and meadow voles are *sympatric*, that is, when they live in the same place, the prairie voles tend to dominate and drive the meadow voles into less desirable, marshy areas (Findley, 1954).

<sup>5</sup> It has been argued that female orgasm occurs only in humans, and it’s hard to prove that’s not true. The licentious bonobo is sometimes held to be an exception, but she may be the exception that proves the rule. The argument is associated with Desmond Morris, who proposed that the female orgasm has evolved to enhance the monogamous pair bond and make family life more rewarding. According to Morris, only a long-term, stable male partner knows how to make a particular woman climax properly. (Hmpf.) The events that occur during female orgasm are known to enhance sperm transport and thus, fertilization of the egg. To biologists, it is a way for a woman to reward a man who pleases her. To which Edmund Spenser replies: *And all for love, and nothing for reward.*



TOADFISH. VASOPRESSIN MAKES HIM GRUNT. OXYTOCIN MAKES HER GRUNT.

In humans, the peripheral effects of oxytocin are contraction of the uterus and ejection of milk. What oxytocin does when it acts in the brain is more interesting; it activates the formation of social bonds.<sup>6</sup> Most of the relevant research has been done in lower animals, where oxytocin has a decidedly prosocial effect. When scientists inject oxytocin into the brains of rats or sheep, for example, it induces maternal and reproductive behaviors. Oxytocin contributes to partner preference in our faithful friend the prairie vole. If you stimulate oxytocin in a prairie vole's brain, she will mate for life with any male who happens to be there at the time. If you block oxytocin in her brain, she won't give him a tumble.<sup>7</sup>

We don't know nearly so much about such effects for oxytocin in humans, but we know enough. For example, female orgasm releases oxytocin in the brain, which may be another reason why women prefer men who pleasure them well. Women who had higher oxytocin levels early in pregnancy and during the post-partum period show more maternal behaviors like affectionate gazes and caresses and pleasant thoughts of being in love. They even check their babies more frequently. (R. Feldman, Weller, Zagoory-Sharon, & Levine, 2007) There are different variants of the oxytocin gene (alleles), and depending which allele a woman has, she will be more, or less sensitive to her toddler. (Bakermans-Kranenburg & van Ijzendoorn, 2008) Even in women who are not pregnant or post-partum, higher oxytocin levels are strongly associated with attachment behaviors, like the proclivity to share feelings with close friends. (Tops, van Peer, Korf, Wijers, & Tucker, 2007). In men and women, higher oxytocin levels are associated with affectionate feelings about one's own parents, less psychological distress and less depression. (Gordon et al., 2008) Administering oxytocin increases feelings of interpersonal trust (Kosfeld *et al.*, 2005). And so on. In humans, prairie voles, rats, sheep and toadfish, oxytocin is important for intimacy, trust and affection. (Bakermans-Kranenburg & van Ijzendoorn, 2008)<sup>8</sup>

<sup>6</sup> (Carter, 1998)(Carter & Altemus, 1997)

<sup>7</sup> [Lim et al. 2004](#); [Williams et al. \(1994\)](#); [Young et al. 2001](#); [Lim et al. 2004](#)

<sup>8</sup> On the pathological side, psychiatrists have determined that some patients with autism and schizophrenia have aberrant expression of the oxytocin gene, and this may account for their aberrant social and emotional behavior. They have reported some success improving the social behavior of these patients with intranasal oxytocin sprays. (Lee, Macbeth, Pagani, & W. S. Young, 2009) (E Lerer et al., 2008) (Kéri, Kiss, & Kelemen, 2009)

Oxytocin release is stimulated by various types of pleasant sensations like warmth or a gentle caress. Eating food triggers oxytocin release. All of the simple, happy events of daily life activate the oxytocin system.(Uvnas-Moberg & Petersson, 2005) (Cyranski et al., 2008)<sup>9</sup>

There are weeds in the oxytocin garden, however, and they speak to interesting aspects of the psychology of women, hitherto unexplained. For example, although oxytocin is a prosocial and anti-stress hormone, especially in females, it behaves quite oddly in response to social stress. Women in the midst of relational distress have high levels of oxytocin. This does not occur in response to other forms of stress, just interpersonal stress.(Tabak, McCullough, Szeto, Mendez, & McCabe, 2011) The phenomenon has been expanded upon by Shelly Taylor and her colleagues (2000) at UCLA, who proposed that women respond differently to interpersonal stress, compared to men. She reiterated the old saw we learned in High School biology about the stress response: “fight or flight.” But that response, she thinks, is more characteristic of men. In women response to social stress is what Taylor calls “tend and befriend.” She explains:

*Tending involves nurturant activities designed to protect the self and offspring that promote safety and reduce distress; befriending is the creation and maintenance of social networks that may aid in this process. The biobehavioral mechanism that underlies the tend-and-befriend pattern appears to draw on the attachment-caregiving system, and neuroendocrine evidence from animal and human studies suggests that oxytocin, in conjunction with female reproductive hormones ... may be at its core.(S E Taylor et al., 2000)*

The way a typical female response to social stress, like a marriage that is falling apart, is to cultivate her “affiliative connections,” especially with other women. Sisterhood promotes safety and relieves distress. Women in such circumstances generate high levels of oxytocin. As a prosocial hormone, it is a marker of her drive for affiliation. As an anti-stress hormone, it is a physiological mechanism for reducing the stress of relational disruption. (Shelley E. Taylor, 2006)

This same pattern, incidentally, occurs in children. An infant girl, in response to a cruel or uncaring mother or an abusive father, generates increased bonding behaviors, as if she were trying to win her parent back. An infant boy is more likely to become detached and disinterested. Little girls evidence more nurturant behavior to their mothers, especially abusive or defective mothers, while little boys are more likely to be hostile and disruptive. In response to abuse, teen-age girls tend to develop excessive and sometimes inappropriate bonding behaviors – sexual promiscuity, teen-age pregnancy – while adolescent boys are more likely to be delinquent.(DAVID & LYONS-RUTH, 2005)<sup>10</sup>

<sup>9</sup> If you breed mice who have no oxytocin at all, they are ineffective mothers, have a lot of anxiety and extreme stress reactions.(Cyranski et al., 2008)

<sup>10</sup> Another paradox of oxytocin as an anti-stress and pro-social hormone is the fact that women with depression have higher levels of oxytocin release, compared to women who are not depressed and to men who are. The paradox is explained, however, by the pattern of oxytocin release. Oxytocin levels in response to pregnancy, maternity and bonding are elevated in a sustained pattern. In the event of depression, or social stress in general, oxytocin release is said to be “dysregulated.” That is, the levels are up and down, more variable from hour to hour.(van Londen et al., 1997)

Depressed women with higher concentrations of oxytocin, compared to those with lower concentrations, report a panoply of interpersonal difficulties: greater difficulties being sociable, greater social avoidance, greater difficulties being assertive, and the tendency to view oneself as being controlling or manipulative. These traits are dysfunctional strategies that aim to achieve closeness in relationships, but they all too often have the opposite effect. Going back to the last section, this constellation of interpersonal difficulties reflects an anxious/ambivalent style of adult attachment, in which individuals desire close relationships yet live in constant fear of rejection or abandonment.(Cyranski et al., 2002)

In a securely attached woman, oxytocin release is calm and measured, promotes affiliation with supportive attachment figures and modulates responses to pain and to stress. In a woman who is depressed and/or in an insecure relationship, oxytocin pulses wildly in a futile attempt to control anxiety and rumination and to repair dysfunctional relationships. When oxytocin-related elevations in affiliative need interact with an insecure attachment style, a woman generates ever more maladaptive coping responses to preserve unsupportive relationships. This, in turn, leads to more pulses of oxytocin

## VASOPRESSIN, AND THEN BACK TO VOLES

Oxytocin and vasopressin are like sister and brother, descended from the same protohormone, and engaged in many of the same functions. They both participate in the broad swathe of behaviors biologists call social communication, and they are both involved in learning, memory and reward. But they exercise their effects in different ways. If oxytocin is from Venus, promoting social behavior in the service of harmony and tranquility, vasopressin is from (you guessed it) Mars. Vasopressin is also central to sexual stimulation, pair-bonding and parental behavior, but it does so in a defensive way, activating arousal, attention and vigilance, increasing the activity of the sympathetic nervous system, and facilitating aggressive behavior. Across species, vasopressin is associated with the regulation of aggression as well as affiliation, but predominantly in males. In males, male animals at least, mating and pair-bonding is usually anteceded by competition with other males, an event that is not infrequently associated with aggressive behavior. (Carter & Altemus, 1997)(de Wied, Diamant, & Fodor, 1993)

The study of vasopressin brings us back to the vole, who, you will remember, is represented by one of most faithful of all mammals (prairie vole) and one of the most promiscuous (meadow vole). The difference between the two is a function of their vasopressin receptor – the molecule on the surface of a neuron that vasopressin attaches to in order to produce an effect. The receptor is **V1aR**, and the behavior of that receptor is regulated by a “microsatellite” in its gene, which is named ***avpr1a***.<sup>11</sup> This microsatellite is like a tail attached to the gene itself and during the course of evolution it has been amplified in the prosocial prairie voles but not in the asocial meadow voles.<sup>12</sup> So, the monogamous prairie vole has a long *avpr1a* allele (more than 600 base-pairs long) while the promiscuous meadow vole has a real short one (about 50 base-pairs). The prairie vole, then, carries a lot more baggage than just a wife and a new litter of pups every month or so, but he doesn’t seem to mind. (Hammock & L. J. Young, 2006)

A longer microsatellite array – a longer tail – increases the number of vasopressin receptors in certain parts of the prairie vole’s brain, thus increasing his sensitivity to the prosocial effects of that neuropeptide. In fact, some prairie vole males have longer microsatellites than others, and the ones that do spend more time in licking and grooming their pups, which is one of the things paternal rodents ought to do. (Hammock & L. J. Young, 2005)

If you inject vasopressin into a meadow vole’s brain not much happens. But, if you (cleverly) insert the *avpr1a* gene into a certain part of the meadow vole’s brain (the ventral pallidum), you get a completely different picture. They grow a whole lot more vasopressin receptors, they spend more time huddling with a single partner

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release and even greater levels of social distress, a vicious circle that leads all too frequently to depression. (Cyranski et al., 2008) Thus, a small peptide hormone reflects a pattern of human behavior with which we are all too familiar.

<sup>11</sup> Microsatellites, also known as Simple Sequence Repeats (SSRs) or short tandem repeats (STRs) or just plain repeats, are repeating sequences of 1-6 base pairs of DNA. On the DNA molecule, the nucleotide adenine (A) forms a base pair with thymine (T) and guanine (G) forms a base pair with cytosine (C). The repeated sequence is often simple, consisting of two, three or four base pairs and can be repeated 10 to 100 times or more. Short tandem repeats used to be considered “junk,” useless stuff that just happens to be on the DNA in between the real genes. In fact, they comprise the better part of the DNA molecule and they influence how a gene is expressed. For example, we all have a fragile X gene (FMR1), and the gene governs the normal development of neurons. Most of us have fewer than 50 CGG (cytosine-guanine-guanine) repeats within the FMR1 gene. A mutation has occurred in this gene, though, and some unfortunate individuals have more than 200 CGG repeats. The normal development of nerve cells in their brains is compromised, and most such individuals are mentally handicapped.

What makes microsatellites useful is the fact that at the same location within the genomic DNA the number of times the sequence (e.g., CGG) is repeated often varies between individuals, within populations, and/or between species. During evolution, genes are “conserved.” That means that the same gene performs the same or similar functions in different species. However, different species and different individuals who share the same gene may differ in the number of microsatellites or repeats they have connected to them, and the number of repeats will effect how the gene itself is expressed. The *avpr1a* gene has been amplified in prosocial prairie voles and consists of several GA repeat. The “asocial” meadow voles do not have many GA repeats at all.

<sup>12</sup> Biologists consider promiscuity “asocial.”

and less time huddling with strangers and when they have pups they spend more time looking after them. (Lim et al., 2004)

As you might imagine, the discovery of a gene, with two versions, a long one associated with fidelity and a short one associated with wanton behavior, elicited the predictable reaction in the press: e.g., *A single “love gene” that transforms Don Juans into loyal and attentive spouses has been identified by scientists, casting fresh light on the chemical cocktail in the brain that ignites romance.*<sup>13</sup> Interestingly, bonobos (*Pan paniscus*) and humans, two primate species characterized by high empathic and sexual bonding, also share a very long tail (869 base pairs, a lot more than even the prairie vole), while the less-empathic chimpanzee (*Pan troglodytes*) only has about 600.(Hammock & L. J. Young, 2006)

Before long, you will be able to genotype your prospective mate, or maybe guys will put their *avrp1a* genotype on a tie, just as they used to wear ties that had little condoms to prove they did safe sex. In this vein, researchers think that a particular repeat sequence on this gene, RS3, can tell you whether or not a cohabiting couple is married, whether or not that have had serious conflicts in their relationship, and whether they were pleased with their mates.(Walum et al., 2008)

Hesse Walum, a geneticist at the Karolinska Institute in Stockholm, was rather proud of his study. *Men with two copies of the allele had twice the risk of experiencing marital dysfunction, with a threat of divorce during the last year, compared to men carrying one or no copies. Women married to men with one or two copies of the allele scored lower on average on how satisfied they were with the relationship compared to women married to men with no copies.* To which Helen Fisher, an anthropologist at Rutgers, remarked: *There are many ways this information can help a man and his wife when they marry. Knowing there are biological weak links can help you overcome them.* A man who knows he has this allele, she said, might be able to use the knowledge to ignore tugs of restlessness he might feel in his marriage: *You can say, 'Oh, it is just my DNA, and I am going to ignore it.'* As if it were that easy.

*What this means is that some people will go into marriage with a stronger deck of cards,* Fisher said. *But there are people genetically prone to alcoholism who give up booze and make a good marriage. No one is saying biology is destiny.* Fisher, who described herself as a romantic, said she would not reject a potential mate who has two copies of the risky allele. She paused, then added: *But I might not start a joint bank account with them for the first few years.*<sup>14</sup>

Variations in this gene also affect a male's scores on the “Pair Bonding Scale.” If you can't get your boyfriend genotyped, then you can give him the PBS. Variations in the gene are also related to the age of first sexual intercourse in men and women (Prichard, Mackinnon, Jorm, & Easteal, 2007); to altruistic behavior in the Dictator Game (Knafo et al., 2008); with liking to dance (Rachel Bachner-Melman et al., 2005); and with liking music (Ukkola, Onkamo, Raijas, Karma, & Järvelä, 2009). These are all activities in which you can productively engage, especially dancing.

Biology is destiny, as a matter of fact. We are biological creatures after all, not angels, and we are born, grow up, mate and die just like every other organism. It may a bit disconcerting to think that everything that happens to us, even the choices we make with our free will, is governed by a bunch of really little things, like mirror neurons, alleles and neuropeptides. It may be disconcerting but it shouldn't be disheartening. Neither is it blasphemous. What makes this discussion interesting is that there are so many bunches of little things that participate in what we think, feel and do. I am going to tell you about a few more, but the goal isn't to make you

<sup>13</sup> *The Sunday Times*, June 17, 2004

<sup>14</sup> Study Links Gene Variant in Men to Marital Discord By Shankar Vedantam Washington Post Tuesday, September 2, 2008

feel like an automaton or a creature of your synapses. Just for a glimpse of my final argument, the biological systems that participate in our thoughts, feelings and behavior have achieved a level of such inordinate complexity and subtlety that they have elevated our being to a level that hovers a bit above biology. We have different names for what that is, but you will have to wait.

When I was a medical student, one of my neurology professors was holding forth. *Outside of the nervous system*, he said, *the only things that happen are that glands secrete and muscles contract*. He went on in this vein, to the effect that there were more *kinds of cells* in the nervous system than the *total number of cells* in the rest of the body. I assumed that he was being hyperbolic, and I must admit that I have never checked his arithmetic, but I assume his point was that the nervous system is a thing of extraordinary complexity and wonder. For the past 40 years I have been dealing with nervous systems, along with the glands and muscles that are attached to it, and I have to agree that my old professor had a point.

Scientists, especially biologists, spend their lives studying very small aspects of complex systems. Thus enthralled, they can overvalue, sometimes, the importance of their small discoveries. Vasopressin and oxytocin and the genes that direct them are important discoveries, but they are only small parts of the picture I am trying to draw. Here are few more small parts before we elevate.

## BRAIN IN LOVE

Here is the constraint a 21<sup>st</sup> century intellectual has to contend with: one isn't allowed to dilate on any aspect of human behavior unless one (a) has a gene for it and (b) has a place in the brain where it happens. As far as love is concerned, we know about at least one gene that lets it happen. But if love is real, our 21<sup>st</sup> century prejudice requires a place for it to happen in the brain. The contrapositive of that statement is that if we can't identify some kind of activity in the brain, then the behavior doesn't really happen. So we should be relieved to learn that love is associated with some kind of activity in the brain. Therefore, love happens. We need that kind of re-assurance from neuroscience, some days more than others.

One of the ways to examine activity in the brain is by means of a number of new technologies that go by the name of functional brain imaging and that include PET, SPECT, functional MRI and magnetoencephalography. They are "imaging" techniques because they generate images of the brain, just as X-rays generate images of bones. They are "functional" because they indicate the activity of brain tissue rather than just its structure, as a CT scan or brain MRI does. Functional imaging is used clinically for the diagnosis and management of cancer, because malignant tissue is more metabolically active than ordinary tissue and manifests a characteristic image during a PET scan. Functional imaging is mostly used as a research tool. As such, it usually generates more information than we know what to do with.

Brain scientists have applied imaging technology to all kinds of love: to romantic love and maternal love; to intense, youthful infatuation and the love of old married couples; to altruism, lust, unconditional love, and what happens when someone breaks your heart. One wouldn't expect brain scientists to display such versatility in their appreciation of affairs of the heart, but there you have it. One is entitled to a degree of skepticism that a small number of boffins – including, by the way, the romantic Dr Fisher – armed with clumsy great machines might achieve insights that have eluded generations of poets and mystics. But it appears that they have. Well, maybe they have. Maybe what they've simply re-discovered what lovers have known all along. The reader can decide for herself. Consider:

1. *There is only one kind of love but there are a thousand different copies.*<sup>15</sup> Considering all the different kinds of love you can imagine, there is a certain commonality in the neural mechanisms behind them. There is a remarkable similarity in the pattern of brain activation produced by viewing the face of a loved partner and the face of a loved child by the mother. There are no differences in the patterns of brain activation between males or females in love or between heterosexuals or homosexuals. What is common to all the studies of love is activation of brain regions that are rich in dopamine and that are central to the experiences of motivation and reward. In spite of the strong commonalities, however, brain activation patterns differ, however, when romantic love is compared to maternal love or to unconditional (saintly) love. (Stephanie Ortigue, Bianchi-Demicheli, Patel, Frum, & Lewis, 2010)
  
2. There isn't a particular place in the brain where love happens. There is a network of brain centers that participate in the experience of love and the act of loving. The core of the network may be in the caudate nucleus in the basal ganglia,<sup>16</sup> the ventral tegmentum and the hypothalamus. These areas are subcortical – parts of the brain that are phylogenetically older, and that we share with higher animals, like parrots, prairie voles and bonobos but also with lower animals, like reptiles. In mammals, however, the network has expanded into brain regions associated with emotional experience. In human, it has expanded into the neocortex. Projections from a lower core area to the frontal and temporal lobes of the neocortex activate areas of the brain that participate in the integration and regulation of emotional events. The frontal cortex in particular coordinates and processes virtually all information that floods into brain, makes judgments and lays plans. Voles and parrots don't have much neocortex at all. Bonobos have some, but not nearly so much as you and I do. (Esch & Stefano, 2005)
  
3. Love is manifest in brain centers with functions that are relevant to the experience of loving. The tegmentum is a central region of the brain's reward system, associated with pleasure, general arousal, focused attention and motivation to pursue and acquire rewards.<sup>17</sup> The caudate nucleus participates in the functions of reward detection and expectation, feedback processing and the integration of sensory inputs to prepare for action.<sup>18</sup> (H. Fisher, Aron, & L. L. Brown, 2005) The hypothalamus is the essential link between the central nervous system and the endocrine system. Activity in the hypothalamus is related with sexual behavior. Projections also occur to areas of the cerebellum that are associated with emotional conditions, especially the recall of emotional memories and empathy with a lover. Another associated cerebellar region seems to play a role in craving, since it has been shown to be active during states of thirst.<sup>19 20 21</sup> (Acevedo, Aron, H. E. Fisher, & L. L. Brown, 2011)

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<sup>15</sup> La Rochfoucauld, *Maximes*

<sup>16</sup> the specific function of the caudate nucleus is to control approach-attachment behavior, ranging from plain approach to a target, to romantic love. (Villablanca, 2010)

<sup>17</sup> Wise 1996; Schultz 2000; Martin-Soelch *et al.* 2001; Schultz 2000; Delgado *et al.* 2000; Elliot *et al.* 2003

<sup>18</sup> Schultz 2000; Martin-Soelch *et al.* 2001; Lauwereyns *et al.* 2002; O'Doherty *et al.* 2002; Zald *et al.* 2004

<sup>19</sup> John 4:13-14: Jesus answered, "Everyone who drinks this water will be thirsty again, but whoever drinks the water I give them will never thirst. Indeed, the water I give them will become in them a spring of water welling up to eternal life."

<sup>20</sup> "Passionate love is a quenchless thirst..." ~ Kahlil Gibran

<sup>21</sup> Shakespeare (Venus & Adonis):

Never did passenger in summer's heat  
 More thirst for drink, that she for this good turn;  
 Her help she sees, but help she cannot get;  
 She bathes in water, but her fire must burn;  
 'O pity,' 'gan she cry, "flint-hearted boy!

4. Love activates certain areas of the brain but it de-activates others. The activation of brain centers having to do with reward and motivation, feedback processing, emotional intensity and craving is balanced by the de-activation of very large regions of the brain, extending from parietal to parts of the frontal and temporal cortex. The regions that love turns off are associated with negative emotions, social judgment and, remarkably but not surprisingly, the proper assessment of other people's intentions and emotions. The brain basis for love has been described as if it were a "push-pull" mechanism that overcomes social distance by deactivating the networks that are used for critical social assessment and negative emotions, while it bonds individuals through the involvement of the reward circuitry. The latter explains the power of love to motivate and exhilarate, the former explains why love is blind.<sup>22</sup> (Bartels & Zeki, 2004)
  
5. Sex and Love: Woody Allen said, *The difference between sex and love is that sex relieves tension and love causes it*. Not quite. The state of love actually mitigates the stress response, while sexual activity sometimes has the opposite response, depending, I suppose, on what you are doing and who you are doing it with.<sup>23</sup> Woody Allen may not be the best authority the subject, anyway. He also said, *My love life is terrible. The last time I was inside a woman was when I visited the Statue of Liberty*.<sup>24</sup>

In any event, love is different from sex drive. Biologists consider sex drive and romantic love to be distinct systems, "designed to orchestrate different aspects of the reproductive process." Now that is a line you may be able to use. The sex drive is what leads people individuals to "initiate courtship behavior," which is another way to put it. Love and attachment motivate them to focus their mating energy, and this, for some people at least, conserves time and metabolic energy. (Fisher 1998)

The sex drive is characterized by the urge for sexual gratification. It is associated with the androgens (e.g., testosterone) in many primates, especially humans. People – men and women -- with higher circulating levels of testosterone tend to engage in more sexual activity. Women tend to feel more sexual desire during and around ovulation, when their testosterone activity increases. Both sexes have fewer sexual fantasies, masturbate less frequently and engage in less intercourse as levels of the androgens decline with age. Androgens are central to the sex drive, but they have never been associated with romantic love. For example, when humans self-administer androgens to boost their sex drive, they do not report that they fall in love. Sex and love are the precincts of two neural systems that do not always act in tandem in *Homo sapiens*. Functional neuroimaging indicates that the sex drive is associated with specific networks of brain activation and that these networks are largely distinct from those associated with romantic love.<sup>25</sup>

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'Tis but akiss I beg; why art thou coy?

<sup>21</sup> " Passionate love is a quenchless thirst...." ~ Kahlil Gibran

<sup>22</sup> The neurobiology of love. *FEBS Letters*, Volume 581, Issue 14, Pages 2575-2579 S. Zeki

<sup>23</sup> Famous people who have died during sex: Nelson Rockefeller, Atilla the Hun, Errol Flynn, David Carradine, at least one French president, Lord Palmersston and a couple of Popes frequent sex. In fact, episodic sexual activity is associated with a threefold increase in the occurrence of heart attack or sudden cardiac death (Dahabreh & Paulus, 2011), about the same risk that is conferred by eating a heavy meal. (Nawrot, Perez, Künzli, Munters, & Nemery, 2011)

<sup>24</sup> He also said, Sex between a man and a woman can be absolutely wonderful - provided you get between the right man and the right woman; and Love is the answer - but while you're waiting for the answer, sex raises some pretty interesting questions; and Sex without love is an empty experience, but as empty experiences go, it's one of the best. For a man who has made such a hash of his own love-life he has some astonishing insights. See Chapter....

<sup>25</sup> [Edwards & Booth 1994; Sherwin 1994; Van Goozen et al. 1997;](#)

Is there anything new in all this? Happily, not. The technical details are credible because they coincide with what we already know. If there were something revolutionary in the brain science of love, it would mean that we have been babbling on for centuries in a completely wrong-headed way.

The technical details are interesting in their own right, though, and they do serve to underscore my argument. Love is represented in the brain and different aspects of love are associated with activity in different brain regions. Love is not localized to a particular place in the brain, but it involves the integration of several neural networks. These networks are based in lower parts of the brain, areas that function in like manner in primates and other mammals and in birds. They are networks that mediate reward, emotion, and motivation. These are the foundations upon which Love has been built. They are very old and very strong, but they are only the foundations.

Animals express emotions in their own particular ways, they are motivated to eat, mate, care for the young and sleep in a comfortable place, and they find all these activities rewarding. Those are the foundations. In humans, however, new structures in the frontal and temporal cortex have been added on. These structures preside over the changes that have occurred during the evolution of *Homo* in the experience of courtship, mating and attachment. More than an instinctive drive or an emotion, our experience of love has become a motivating force of extraordinary power and transcendence. Uniquely in the human beings, courtship, mating and attachment are strongly represented in the areas of brain that govern our motivations and turn them into aspirations. They are areas of brain that subsume our sense of personal reward into the broader interests of our families and communities. Emotions generated in the lower parts of the brain are modified and modulated in the frontal and temporal cortices and are channeled into new and altogether fantastical directions. Love, therefore, is more than an emotional state. (S Ortigue, F Bianchi-Demicheli, A. F. de C. Hamilton, & S T Grafton, 2007) (Francesco Bianchi-Demicheli, Scott T Grafton, & Stephanie Ortigue, 2006) (Aron et al., 2005)

*Beloved, let us love one another: for love is of God; and every one that loveth is born of God, and knoweth God. He that loveth not knoweth not God; for God is love.*<sup>26</sup>

## LOVE POTIONS

Before we start thinking about the music of the spheres and the mutual attraction of heavenly bodies, I need to give you something you can put to practical good use. You have read so much now about the brain in love, genes that make men loyal husbands and neurotransmitters that convey romantic messages, and all the little animals and the strange ways they have. Having gone through all of that, any sensible reader should be asking herself, well, doctor, what can you do about it? Can you write me a prescription?

That's the problem with science. It's very good at coming up with clever ideas, but when it comes to doing something useful with them, it often falls short. What we really need is something to improve our everyday love life. We could really use a prescription for a broken heart or a treatment to help someone fall back in love when he says that he has fallen out of love. It would be great to have a genetical test that will predict whether a man will be a good husband, a reliable father or at least an attentive lover. Or a device that you can fit under a simple black dress with spikes that come out when some creep comes too close, and without damaging the fabric. I have suggested a number of such practical applications of love science during the course of the book, and I can only assure you that my colleagues in the medical device and pharmaceutical industries have been attentive. They ask me, Do you think there is there a market for such a thing? Would it be something like a vaccine that you only

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<sup>26</sup> 1 John 4, 7-8, King James.

have to take once, or like an antibiotic, that you take for 10-14 days? Or would it be a blockbuster like Lipitor or Prozac that you have to take forever? And is it likely to be covered by your medical insurance plan? Of course, they lose interest when the answer to the last question is, probably not. What the great multinational medical device and pharmaceutical companies lack in imagination they more than make up for in their preoccupation with niggling details.

The forays that the Industry has made into the sylvan glade have been, thus far, really limited. They are mainly about sex, not love or marriage, and even there their contributions have been modest. For example, they gave us the birth control pill, which inspired to poet to write:

*Sexual intercourse began  
In nineteen sixty-three<sup>27</sup>*

They have done well with drugs to arrest the spread of sexually transmitted diseases, not an insignificant accomplishment I suppose, given the sexual versatility of the human beings and their determination to spread them. Their most creative contribution to the art of love was discovered quite by accident and its appeal is limited to older men whose members tend to stay limp. Those are phosphodiesterase-5 (PDE5) inhibitors, like Viagra and Cialis,<sup>28</sup> which have a circumscribed effect on the male erection, but little to no effect on complementary problems in females (sexual arousal, orgasm) and no effect at all on sexual desire in males or females. (D. A. Brown, Kyle, & Ferrill, 2009)<sup>29</sup>

In fact, most of the medications Pharma has given us -- blood pressure medications, antidepressants, anti-histamines and tranquilizers -- suppress sexuality in one way or another. And they do it in men and women and at every stage of the sexual cycle: desire, arousal and consummation. I am surprised that no one has ever concocted a conspiracy theory around that. If there is a conspiracy, it is a notable failure. Antidepressants of the Prozac class, the SSRI's, for example, are quite effective at reducing sexual desire, arousal and/or orgasm. The irony is that they hardly ever do so in patients who need to have their mojo turned down: sexual predators, for example, or sex addicts or randy teen-agers.

There are case reports in the medical literature of drugs that increase sexual behavior, but it hardly ever turns out well. L-DOPA and bromocriptine, drugs that increase the activity of the neurotransmitter dopamine, are occasionally associated with compulsive or disinhibited sexual behavior.<sup>30</sup> The antidepressants trazodone and chlomipramine have been associated with yawning + orgasm in females; that is, every time the poor girl yawns, she has an orgasm. This, I am told, is a decidedly unpleasant turn of events. Methamphetamine, cocaine and NMDA are known to increase sexual behavior, at least in the short run; over the longer term, they will blot it out.<sup>31</sup> Just like alcohol:

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<sup>27</sup> Philip Larkin, *Annus Mirabilis*

<sup>28</sup> Sildenafil is a highly selective inhibitor of PDE type 5 (Boolell et al 1996; Gbekor et al 2002). It enhances NO-mediated relaxation of human corpus cavernosum in vitro (Ballard et al 1998; Stief et al 1998; Gemalmaz et al 2001). Sildenafil, by inhibiting phosphodiesterase, increases the intracellular concentrations of cyclic guanosine 3',5' monophosphate (cGMP), causing an amplification of the endogenous NO-cGMP signaling pathway. (Hatzimouratidis, 2006)

<sup>29</sup> For many years gynecologists have used microdoses of male sex hormones to stimulate the libido of female patients complaining of lowered sex interest but their use is highly controversial. Some gynecologists insist that there is much more than a placebo effect in the monthly booster shots of testosterone. The literature is threadbare on this prevalent gynecological practice, the results of which, endocrinologists say, spill into their offices when the annoying virilizing signs appear.

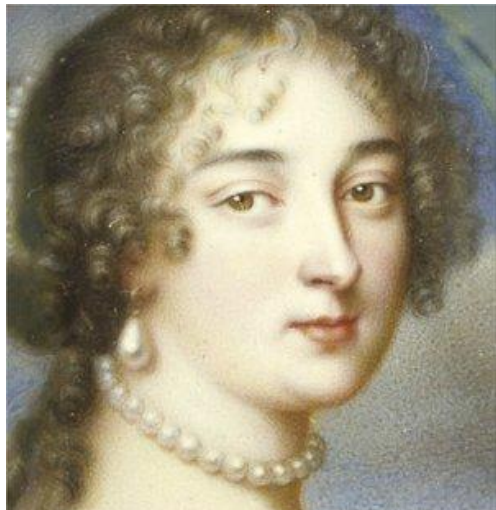
<sup>30</sup> Bromocriptine and cabergoline are advertised on the Internet as "sensational sex drugs" because they inhibit the activity of prolactin, a pituitary hormone that suppresses sexuality. Prolactin is secreted in large amounts during breast feeding.

<sup>31</sup> Meth is one of the most abused illicit drugs in the World (NIDA, 2006, Ellkashaf et al., 2008) and it has been frequently linked to altered sexual behavior. Interestingly, Meth users report heightened sexual desire and arousal, as well as enhanced sexual pleasure (Semple et al., 2002, Schilder et al., 2005). Moreover, Meth abuse is commonly associated with sexually compulsive behavior (Rawson et al., 2002). Users often report having numerous sexual partners and are less likely to use protection than other drug abusers (Somlai et al., 2003, Springer et al., 2007).

*Macduff. What three things does drink especially provoke?*

*Portyer. Marry, sir, nose-painting, sleep and urine. Lechery, sir, it provokes, and unprovokes; it provokes the desire, but it takes away the performance; therefore, much drink may be said to be an equivocator with lechery: it makes him, and it mars him; it sets him on, and it takes him off; it persuades him, and disheartens him; makes him stand to, and not stand to; in conclusion, equivocates him in a sleep, and, giving him the lie, leaves him.<sup>32</sup>*

The world history of love potions goes a long way back. Leah used mandrake roots to seduce Jacob (Genesis 30). Tristan and Iseult fell in love because of a potion they drank. A love potion made from pansies drives much of the action in A Midsummer Night's Dream. The madness of Caligula was attributed to love potions his



Madame de Montespan (1641-1707), mistress of Louis XIV, gave him a love-potion made from frog excrement. They had seven children together.

wife, Caesonia, gave him, but she managed to keep his attachment, for what it was worth, until the end of his life. Madame de Montespan was so jealous of her rivals for the affection of Louis XIV that she poured a love potion made of frogs' excrement (sic) into his wine, and for no fewer than thirteen years. When he found out, he was really angry, and sent Madame de Montespan away, but not before she had given him seven children.

Love potions in history and literature are designed to incite romantic love, or *eros*; the legends were fueled by the fact that some natural substances, like yohimbine and nutmeg can stimulate penile erection, clitoral engorgement or the like. Ginseng, for example, has a reputation in traditional Chinese medicine for treatment of sexual impotence. Recent studies in laboratory animals have shown that both Asian and American forms of ginseng enhance libido and copulatory performance. Indeed, there is good evidence that ginsenosides can induce vasodilatation and relaxation of the penile corpus cavernosum.<sup>33</sup>

The mandrake plant, popularly known as the 'love apple,' was so-called, it is said, because the shape of the forked roots resemble the lower parts of a human body. In fact, mandrake root extract can cause priapism.<sup>34</sup>

Bufo toad skin contain bufotenine, a substance related to serotonin that causes hallucinations (an "hallucinogen"). It is the active ingredient in West Indian "love stone" and the Chinese medication *chan su*. The aphrodisiac properties, if they exist at all, are presumed to occur in the central nervous system. Cantharidin ("Spanish fly") is a chemical with vesicant properties derived from blister beetles, and it has been used for millennia as a sexual stimulant. Spanish fly works by inhibition of phosphodiesterase activity, the same as Viagra. In Malaya and in Mexico they are said to eat the beetles live.<sup>35</sup> (Sandroni, 2001) Many of the dietary supplements that are sold as "natural aphrodisiacs" actually contain small doses of PDE5 inhibitors, that is, drugs like Viagra. (Csupor et al., 2010)

Other substances have been associated with sexual disinhibition, most notably alcohol, of course. The dancing mania during the middle ages was possibly related to ergot mycotoxins (related to LSD).<sup>36</sup> Other drugs,

<sup>32</sup> MacBeth, Act 2, Scene 3. "Nose-painting" alludes to the fact that drinking a lot makes your face flush.

<sup>33</sup> The amount of ginseng in a bottle of green tea is decidedly subtherapeutic in that regard.

<sup>34</sup> The Hebrew word for mandrake is cognate to the word for lover.

<sup>35</sup> In Southeast Asia, Palembang dermatoided, and in Mexico, the triatomids.

<sup>36</sup> Between 1085 and 1927, epidemics of "convulsive ergotism" were widespread east of the Rhine in Europe due to consumption of grain contaminated with ergot, which is produced by the fungus *Claviceps purpurea*. West of the Rhine, consumption of ergot-contaminated food caused epidemics of gangrenous ergotism. The clinical features of convulsive ergotism--muscle

like caffeine and guarana, have general stimulating effects. Combining an energy drink like Red Bull with alcohol keeps you awake so you can act out your disinhibitions.

All of the love potions people have discovered over the millennia have been nothing more than sexual stimulants of one sort or another. Nothing has ever been discovered that acts like the potion that Tristan and Iseult drank, leading to a deep, abiding but entirely virtuous and unending love. The prairie vole falls in love with a male if a small drop of his urine is put on her nose. But she is a simple beast, with few ambitions and a limited horizon. The love of human beings seems to be too important to be left to molecules.

Speaking of voles, what about those fabulous neuropeptides, oxytocin and vasopressin? Well, oxytocin doesn't get into the brain very easily, and it is mainly used, clinically, for its peripheral effects. But if you take the nasal spray, or, better yet, give it to somebody else, interesting things happen. (Carter & Altemus, 1997) Under the influence of oxytocin, people tend to regard other people as more attractive. That is, the people who have been given oxytocin think that other people are more attractive, whether or not the other people have taken oxytocin or not. None of our scientist friends have thought to see what would happen if everyone were to sniff oxytocin at the same time, but theoretically we would see an outburst of affiliative behavior that would rival the Woodstock festival. (Theodoridou, Rowe, Penton-Voak, & Rogers, 2009)

So far, so good. Here is another interesting effect: oxytocin enhances trust. It hasn't been approved for the purpose by the regulatory authorities, but we know that it happens from experiments with normal volunteers playing various kinds of "economic games." (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) These are games in which money is at stake. Players are rewarded for cooperation, or deception, or some such thing, depending on how the game is set up. In one particular game, players who were given oxytocin demonstrated the remarkable propensity of entrusting their money to other players. That may not be such a good thing, I think, because under the influence of the drug, players may persist in entrusting their money to other players even when the latter have proven to be untrustworthy. (Mikolajczak, Pinon, Lane, de Timary, & Luminet, 2010) (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008)

In other games, oxytocin may increase trust and social cooperation but it only does so within limited borders. In contrast to Woodstock, the effects of oxytocin are positive only in circumstances when player A, who gets the nasal spray, is familiar with subject B. (Declerck, Boone, & Kiyonari, 2010) A dose of oxytocin increases cooperation, but only if the players in the game are familiar with one another. If they know nothing about one another, the drug has no such effect; in fact, they behave much more cautiously.

A discerning reader will note the contradiction in the last two paragraphs. In one study, oxytocin makes you "trust the untrustworthy." In another, you will trust him as long as you know him, whether he is untrustworthy or not. Such contradictions are only to be expected when conclusions are drawn from small studies that no one else bothers to replicate.<sup>37</sup> Nevertheless, we know from studies of animals like the voles that oxytocin

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twitching and spasms, changes in mental state, hallucinations, sweating, and fever lasting for several weeks--suggest serotonergic overstimulation of the CNS (ie, the serotonin syndrome). The ergot alkaloids are serotonin agonists. Dihydroergotamine binds to serotonin receptors in the dorsal horn of the spinal cord, which is the site of neuropathological changes in convulsive ergotism. Dihydroergotamine given to human beings can cause the serotonin syndrome. Ergots produced by different strains of *Claviceps purpurea*, and those growing in different soils, may have different ergot alkaloid compositions. An alkaloid, present in high concentrations in ergots from east of the Rhine, may have caused convulsive ergotism at a circulating concentration insufficient to produce peripheral ischaemia. The serotonin syndrome may, therefore, have been a public-health problem long before it was recognised as a complication of modern psychopharmacology. (Eadie, 2003)

<sup>37</sup> It is ironic, that if a pharmaceutical company wants to make a therapeutic claim for a new drug, it has to perform a series of duplicative studies in varied groups of people in countries around the world. When my colleagues and I developed a cognitive test to use in clinical trials of new drugs, we had to have it translated into no fewer than 57 languages. But if an academic wants to make a claim concerning the human condition, all he needs to do is dun a few undergraduates into subjecting themselves to an experiment in the psychology lab in the basement. He refers to "normal volunteers" is his

and even vasopressin promote trusting and cooperative behavior among individuals within a social group but not towards conspecifics who are beyond the pale. Far from being a “happiness molecule” or an indiscriminate “love drug,” therefore, our two neuropeptides seem to be agents of “in-group favoritism,” “parochial altruism” or even “ethnocentrism.” As such, they may as often be the occasion of cruelty and violence as of love and cooperation. (De Dreu et al., 2010)

The lesson is that human beings, even college students dunned into participating in psychology experiments, are a bit more complicated than voles, and perhaps less predictable. Another lesson is that oxytocin may not be a “molecule of happiness” after all. Psychiatrists have actually tried to use it for therapeutic purposes, in patients who have extraordinary difficulties with trust and interpersonal cooperation; patients with autism, for example or with the borderline personality disorder. The results of oxytocin treatment in these patients are unpredictable and the treatment is hardly ever helpful. (Bartz and Hollander, 2006; Bartz et al., 2010)

## LOVE AND SEROTONIN

The scientific horizon for a love drug, however, may not be nearly so bleak. In fact, the near horizon is rich with possibilities, if we only learn to think about them in the right way. There are plenty of drugs that facilitate affiliative behavior. They have been approved by the regulative authorities and you can get a prescription. But I’m afraid you’re in for an anticlimax.

Most of the drugs we psychiatrists use to treat anxiety, depression, mood instability, psychosis, etc., allow patients with those conditions to calm down and participate in the social life of their families and communities. Men who are prone to explosive attacks of irrational rage can, some of them at least, be successfully managed with a number of different drugs, albeit at the risk of hair-loss, obesity, tremors and memory loss. But that’s his problem, right? Women who are so intolerably anxious they nag like shrews or who get unduly suspicious simply because their poor husbands arrive home five hours late with alcohol on their breath and lipstick on their collars, can be successfully treated in like manner. Such small triumphs of the therapeutic arts fill a psychiatrist with no less than a sense of accomplishment. Their grateful patients shower them with gifts and publish encomia on the Internet. Sample from [www.ncneuropsych.com](http://www.ncneuropsych.com):

*I used to raise hell when Dexter went out to the road-house and came home drunk every night. Since I been to Dr Gualtieri, he gave me massive doses of antidepressant and mood-stabilizing drugs and now I don't give a dam.*

Clearly a therapeutic triumph and a shaky marriage has thus been saved. Not exactly a love potion, but why complain? We psychiatrists can exercise an indirect effect, but that is better than no effect at all. Love can be salvaged when a mental illness is put into remission, but drugs don’t cause love or increase it or make it come back. They simply remove obstacles that stand in its way. In all of the preceding chapters, I enumerated the untoward psychological traits that make for marital unhappiness; since drugs can ameliorate at least some of those traits, they might can, sometimes, promote marital happiness.

*Hello, Mr So-and-so, and why are you here to see me today?  
My wife said I had to come.*

Mental illness is not the cause of every divorce but the traits that are common to mental illness certainly contribute to marital discord and divorce. This fact was articulated by the American psychologist, Lewis Terman,

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publication, assuming, of course, that the college students are “normal” and that they haven’t blasted their brain cells the night before playing beer pong or smoking cannabis, and assuming they are “volunteers” when, in fact they are participating only under pain of opprobrium and faculty recrimination. There is an explanation of course. A new drug, poorly vetted, may be dangerous. Commentary on the human condition is harmless, or mostly harmless.

who performed a seminal study of marital unhappiness in California in 1938. It was a time when the inhabitants of that state were probably more representative of the human condition than they are today, and Terman's study was the first time in history that a scientist used objective tests and statistical methods to evaluate the problem of marital unhappiness. The characteristics of people who were divorced or unhappily married, he found, ought to be quite familiar to my readers. He wrote:

*It is especially characteristic of unhappy subjects to be touchy or grouchy; to lose their tempers easily; to fight to get their own way; to be critical of others; to be careless of others' feelings; to chafe under discipline or to rebel against orders; to show any dislike that they happen to feel; to be easily affected by praise or blame; to lack self-confidence; to be dominating in their relations with the opposite sex; to be little interested in old people, children, teaching, charity, or uplift activities; to be unconventional in their attitudes toward religion, drinking and sexual ethics; to be bothered by useless thoughts; to be often in a state of excitement; and to alternate between happiness and sadness without apparent cause.*

Some notable personality characteristics were identified by Terman, for example, selfishness, lack of tact and indiscipline. But what are especially notable among his unhappy subjects are the characteristics of mood disorder: irritability, anxiety, depression, explosive temper, mood swings. Granted, the study was done 80 years ago, but that, if anything, should increase our confidence in the results. The qualities he described are still very much with us.

It may sound redundant to aver that a bad mood is a cause of marital unhappiness but there is no question that an upbeat, positive mood can help overcome the squabbles and misunderstandings that inevitably occur when two human beings are resolved to spend 50 years or so in close proximity. So, if only the psychiatrists could come up with something to give a person a more upbeat, positive mood, that would be a *good thing*. Something, for example, that would make one less grouchy and more interested in old people, children and uplift activities.

As a matter of fact, they have been working on it for a long time although it wasn't until 1986 or so that they came up with a good candidate. They had been using antidepressants, as they called this class of molecules, for more than thirty years, but the ones they had, like imipramine and iproniazid, had so many unpleasant side effects it was hard to convince people to take them even when they were depressed. No one ever thought to give them to people who were just grouchy or bothered by useless thoughts. In fact, if you gave those drugs to people who were not depressed, to normal volunteers for example, their moods were not uplifted even to a small degree. They just felt kind of sick. All of that changed, of course, when a new class of antidepressant molecules was introduced during the 1980's. These we call the selective serotonin re-uptake inhibitors, or SSRI's, and among them, Prozac pride of place. There are several now to choose among: Paxil, Zoloft, Luvox, Celexa and Lexapro. The last, Lexapro or escitalopram, is the most popular these days because of its efficacy and comparatively low rate of side effects.<sup>38</sup>

The extraordinary characteristic of the SSRI's (or serotonergic antidepressants) is that they have mood-elevating properties even in people who are not especially depressed. Not the euphoriant properties of amphetamine, which are intense but short-lived and ultimately counter-productive, but a more sustained, upbeat and positive mood. We use SSRI's, for example, to help caregivers: people who have to look after a severely handicapped child or a spouse with a deteriorating condition, and who, over the years get tired, exhausted and even demoralized. Some clinicians call this caregiver "burn-out" but it's really just a state of emotional exhaustion. For such a person, a small dose of SSRI is like a vitamin to increase her emotional resources. She isn't depressed, although she often feels a bit ashamed of herself. She is doing God's work, after all, and the decision to do it at

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<sup>38</sup> By the time this is published, escitalopram will have gone generic. I am not on the take.

one time gave her Joy. She ought to feel joyful, but now she is just tired and grouchy. The day-to-day grind tends to have its way with Joy.

We would never think to give such a person a nasal spray of oxytocin to improve her affiliative instincts. But we are pleased to have a drug that increases the activity and efficiency of the neurons in her brain that extrude or receive a neurotransmitter called serotonin.

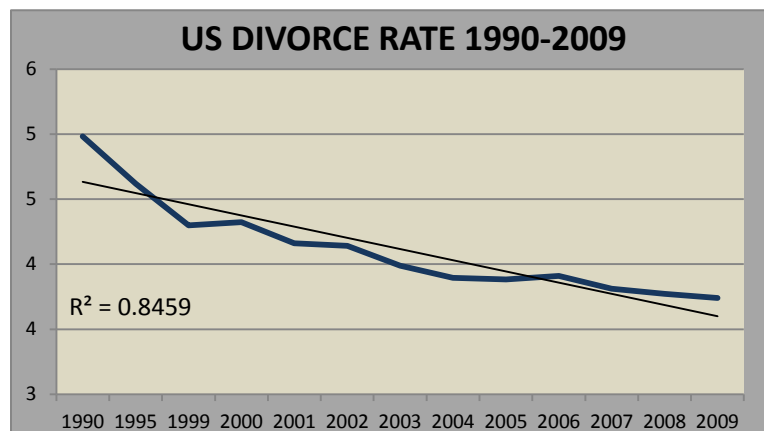
Serotonin is another one of governing neurotransmitters that I talked about earlier, like dopamine, norepinephrine and acetyl choline. It is richly distributed in brain regions that serve reward and motivation, like the caudate nucleus. It also has effects on what are called “appetitive functions” of the brain, and this reflects its origins in the gut. In fact, most of the serotonin in the human body is found in the gut, where it modulates intestinal activity. Thus, appetite and satiety and also sleep are influenced by serotonergic neurons in the brain. Serotonin is synthesized in the body from the amino acid tryptophan; milk is rich in tryptophan, and that’s why people often drink a big glass of milk before they go to bed. Carbohydrate-rich meals promote the movement of tryptophan into the central nervous system, where it turns into serotonin, and makes one sleepy. So, after a big Sunday dinner of spaghetti and meatballs, the men of my family retired to the living room to loosen their belts and sleep for a bit. Red wine may have had something to do with it, too.

Meanwhile, as the men slept, the women would be in the kitchen, having a much better time cleaning up and chatting away, mostly about their husbands and children, and about other women and their husbands and children. They weren’t sleepy but were, rather, enjoying the well-being that comes of a carbohydrate load, tryptophan transport, increased serotonin in their brains and a strong cup or two of post-prandial Italian coffee. Serotonin, you see, has positive effects on mood. It promotes a sense of well-being, an appetitive form of happiness that we know as contentment.

Not only do the serotonin networks in the brain mediate mood, they also regulate our emotional responsiveness, mostly in a positive direction. They influence our emotional expressions and our willingness to act in accord with them. (D. H. Skuse & Gallagher, 2011) They reduce our reactivity to negative or unpleasant experiences and lend a positive valence to our response to ordinary events. (Kemp, Gray, Silberstein, Armstrong, & Nathan, 2004) Almost all of the psychological traits or psychiatric disorders that make a relationship impossible to endure can be corrected with the right dose of an SSRI: anxiety, depression, irritability, angry outbursts, obsessive jealousy, pessimism, negativism, hatred.

Even in normal healthy people, increased levels of serotonin decreases quarrelsome behavior, lessens one’s responsiveness to quarrelsome behavior in other individuals and enhances one’s attention to positive emotions (Moskowitz, Pinard, Zuroff, Annable, & S. N. Young, 2003) (B Knutson, O M Wolkowitz, et al., 1998) (Harmer, Shelley, Cowen, & Goodwin, 2004) If, on the other hand, you reduce serotonin levels, in people or in animals, you will see all manner of unpleasant events, including depression, irritability, defensiveness, aggression, violent behavior and early death. Monkeys with enhanced serotonin spend more time with their friends, huddle closer and groom a lot, but if you deplete the serotonin they have in their little brains, they become hyperactive and fight all the time. (Brian Knutson, Owen M. Wolkowitz, et al., 1998)

The SSRI’s are an efficient way to increase the activity of serotonin in the brain. Their reliable clinical effects are to reduce negative behaviors like depression and hostility and to activate feelings of well-being. They generate a positive perspective on the behavior of other people. Taking an SSRI is such a common event – if you aren’t taking one yourself, you know someone who is – that we tend to take them for granted, or even grouse about how many people are on them. Instead, we ought to be profoundly grateful that such molecules exist. They have saved a lot of shaky relationships. In fact, since the SSRI’s were first prescribed, the rate of divorce in the USA has declined dramatically:



The chart on the left is taken from the National Center for Health Statistics, and represents data from 44 of the states and the District of Columbia over a 20 year span. Over this period, the divorce rate has fallen from 4.98 per thousand Americans to 3.74, a 25% per cent decline. During that same period, the SSRI's came into common use, and the number of Americans taking the drugs has doubled and then doubled again.

My wife, who happens to own a French restaurant, is not impressed. She points out that a number of other things have changed over the past 20 years. People are drinking more wine, for example, she says, and dining out more. My brother-in-law, who owns a gun shop, claims that husbandly misbehavior has been sharply reduced since more women are armed with the new automatic pistols, designed especially for a woman's hand. I suppose that the declining divorce rate is attributable to a number of factors. Perhaps it has to do with the fact that people are marrying at an older age now, or perhaps it is because fewer people are electing to marry in the first place. If you type in "why the divorce rate is going down," you will get more than two and a half million hits and I'm sure there are at least that many theories, but I am going to stick with the SSRI's.

Is serotonin, then, the "love molecule" we have been looking for? Maybe so, but you can't tell just from the SSRI's. A positive perspective towards the behavior of another person is a necessary condition for love, but is it sufficient? Drugs that amplify the effects of serotonin in the brain make us feel better about ourselves and less bothered by all the annoying things our nearest and dearest conspecific does, but that is not love. I have had patients who report deeper feelings for their loved ones while they are taking an SSRI, or more intense spiritual experiences when they go the church, but that is not a very common event. One is more likely to hear complaints of emotional blunting: *I am less depressed but I think that is because I am feeling hardly anything at all.*

For all the bilge that has been written about Prozac and the others, no one that I know has ever claimed it is a "love drug." The SSRI's certainly don't make you sexually disinhibited, which is what passes for love in some quarters at least. Quite the opposite. The serotonergic antidepressants have a decidedly adverse effect on sexuality. The paradox of serotonin is that enhancing its activity, with drugs like Zoloft, Prozac or Lexapro, tends to reduce sexual behavior, suppressing, in equal measure but in different patients, desire, ability and consummation. With respect to sexual behavior, it has an effect opposite to dopamine. Sometimes, we have luck with the antidepressant bupropion, which stimulates dopamine, when we try to correct the sexual side effects of SSRI's.

Serotonin does decrease sexuality, which is why SSRI's suppress sexuality, but, paradoxically, it increases affiliative behavior and decreases aggression, which makes you or your mate a lot easier to live with. It is a paradox: a brain substance that decreases sexuality increases affiliative behavior. A dirty trick, if you will, until you consider exactly how serotonin is involved in sexuality. Dopamine, as we know, is central to copulation and to most of the events that lead up to it, but serotonin is not released in the brain until orgasm occurs. So, if dopamine is the agent of sexual desire and performance, serotonin is the agent of satiety. (Hull et al., 1999)

Increased serotonin activity following orgasm has some nice effects. It makes one a bit sleepy. It reduces stress. And it makes you want to smoke.<sup>39</sup> More to the point: the release of serotonin in the hypothalamus stimulates oxytocin. Thus, the affiliative and antistress actions of oxytocin come into play.

A drug that stimulates serotonin activity in the brain can go a long way towards salvaging an unhappy marriage doomed to failure. But the result could be a happy marriage without sex, a contradiction in terms, if you ask me, but to a lot of people it's probably an OK trade-off. So, serotonergic drugs are good to have around but they are imperfect candidates for a love potion.

Nevertheless, the idea that love in its deep sense may be somehow related to serotonin is not so outlandish. Oddly, the evidence for this lies in the experiences of people who ingest hallucinogenic compounds that are derivatives of serotonin: notably MDMA ("Ecstasy") and LSD. Both have been called, at one time or another, "love drugs," and not necessarily because they induce a state of sexual disinhibition, although they can do that. Rather, they are associated with ecstatic or transcendent feelings, sometimes feelings for another person, but often feelings of a spiritual nature:

*A Benedictine monk explained that "Ecstasy opens up a direct link between myself and God". He had only taken Ecstasy with a small group of like-minded people in pursuit of prayer. "Ecstasy has the capacity to put one on the right path to divine union... Indeed it was an amazing grace, that grace that passes all understanding. I was moved; I was in communion with everyone else in the room. It was as if, at that moment, all barriers had come down, all suffering had ended, all pain had been relieved, all joys had been known. I forgave the offences I had suffered and was forgiven for my sins. I was healed. I was strengthened. I was redeemed..."<sup>40</sup>*

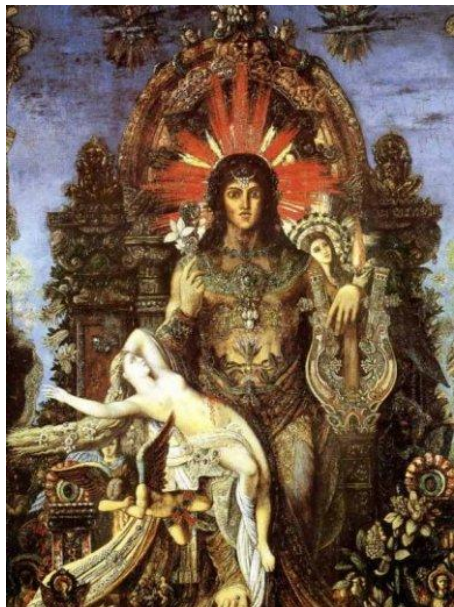
Although religious ecstasy is a step or two away from romantic love, the neurobiology of spiritual rapture tells us something about love in general and love potions in particular. One lesson it teaches us is no less than ironic: the very drugs, like MDMA and LSD, that induce feelings of transcendent oneness with Humankind and the Universe are also the most neurotoxic of all the "recreational drugs." Neurotoxic means that they kill brain cells. This, one has to admit, is an extraordinary coincidence.

The SSRI's are remarkably safe, and they actually improve the condition of patients recovering from brain conditions, like stroke or brain injury. MDMA, LSD and all their hallucinogenic relatives are also stimulators of serotonin activity in brain, but in a different way: they do it in a manner that damages and ultimately kills neurons. This we know from studies of animals who are administered the drugs, and also from cognitive studies of human beings who have taken them for fun, and who are usually found to have deficits in cognitive functions like memory and reaction time that probably weren't there before. A little stimulation of serotonin is a good thing, therefore, but the massive efflux of serotonin molecules into the synaptic cleft that happens when you ingest an hallucinogen causes what neuroscientists call "excitatory neurotoxicity." The lesson is that you can excite your brain only so much before you reach a point of diminishing returns, which is something that I heard once from my mother, although not quite in those words.

An ecstatic state of immersion in Divine love is something to which some of us aspire, but the best we can achieve with these so-called love drugs is a transient experience that leaves one with an awful headache and a few less brain cells. It is as if God doesn't really want us to know him as He really is, or, perhaps He just wants us to work a bit harder before we do. The Greeks knew that. They have a couple of good stories to prove the point.

<sup>39</sup> The urge to smoke after sexual activity is probably mediated by serotonin, just as the urge to smoke after eating. Dopamine tends to reduce the urge to smoke, which is why doctors prescribe Bupropion to help people stop smoking. People hardly ever have the urge to smoke during foreplay because dopamine is active and they hardly ever feel hungry after sex because serotonin induces satiety.

<sup>40</sup> The Agony and Ecstasy of God's path Nicholas Saunders The Guardian, 29/7/95



The prophet Tiresias is said to have stumbled across Athena as she was bathing. When he saw her nakedness he was immediately struck blind. It wasn't his fault, of course, he was just happening by, and she was bathing in a more or less public place. She wasn't trying to punish him, either, it just happened. In fact, she felt so bad about what happened to him, she gave him the gift of prophesy. So it was Tiresias the prophet who told Oedipus that he really didn't want to know who had killed the king of Thebes, who happened to be, of course, his father. (Oedipus' father, not Tiresias'.)

Then there was poor Semele, who enjoyed a brief love affair with Zeus, who disguised himself for the purpose as a mortal man. Zeus' wife, as you can imagine, was angry at Semele. (She was always angry at Zeus.) Hera wiled herself into Semele's good graces and convinced the stupid girl to ask Zeus to show himself in his true, divine form. Semele did just that, Zeus tried to talk her out of it, but she insisted, so he did. Ovid tells us, *Her mortal form could not endure the shock and she was burned to ashes in his sight.*<sup>41</sup>

Drugs that evoke the sense of the Divine presence are called *entheogens*, and there are several of them. Entheogen is a Greek neologism, made up in 1979, but Tiresogen or Semelogen would be better. I don't mean to be melodramatic about all this, but the point is obvious: ecstasy is not a mental event that the brain can sustain for a very long time. Experiencing oneness with the universe and love for all mankind isn't something that you want to do all the time. It burns you right up. Happily for us, love, real love, is not ecstasy, although it does make us feel real good sometimes. It is not an altered state of consciousness. Love is best experienced in its ordinary mortal form.

The idea that ecstasy is entrée to the Divine presence is absurd anyway, just as the idea that love itself is an ecstatic state. God, like love itself, speaks in a still, small voice:

*The Lord passed by, and a great and strong wind rent the mountains, and brake in pieces the rocks before the Lord; but the Lord was not in the wind: and after the wind an earthquake; but the LORD was not in the earthquake: And after the earthquake a fire; but the Lord was not in the fire: and after the fire a still small voice. 1 Kings 19:11-12*

Love is not infatuation. Like the nearness of God, it is an ordinary, everyday thing, and to appreciate it, one has to be still for a moment and reflect quietly. Infatuations inevitably burn out, though they don't necessarily kill brain cells when they do. Love conveys a calm sense of well-being and a cheerful tolerance for the people we love. That is, of course, what an SSRI will do, ideally. So maybe love does have to do with serotonin. Just the right amount of serotonin, stimulated in a still, small way.

<sup>41</sup> It turned out, by the way, that Zeus and Semele had a baby, a boy, who was Dionysius to the Greeks and Bacchus to the Romans, the god of wine.

Depressing List of Medications and Substances That May Cause or Contribute to Erectile Dysfunction (Heidelbaugh, 2010)

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<b>Medication class or substance</b>	<b>Examples</b>
Analgesics	Opiates
Anticholinergics	Tricyclic antidepressants
Anticonvulsants	Phenytoin (Dilantin), phenobarbital
Antidepressants	Lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants
Antihistamines	Dimenhydrinate, diphenhydramine (Benadryl), hydroxyzine (Vistaril), meclizine (Antivert), promethazine (Phenergan)
Antihypertensives	Alpha blockers, beta blockers, calcium channel blockers, clonidine (Catapres), methyldopa, reserpine
Anti-Parkinson agents	Bromocriptine (Parlodel), levodopa, trihexyphenidyl
Cardiovascular agents	Digoxin, disopyramide (Norpace), gemfibrozil (Lopid)
Cytotoxic agents	Methotrexate
Diuretics	Spironolactone (Aldactone), thiazides
Hormones	5-alpha reductase inhibitors, corticosteroids, estrogens, luteinizing hormone-releasing hormone agonists, progesterone
Illicit drugs, alcohol, and nicotine	Amphetamines, barbiturates, cocaine, heroin, marijuana
Immunomodulators	Interferon-alfa
Tranquilizers	Benzodiazepines, butyrophenones, phenothiazines

## PAIR BONDING SCALE

Walum *et al.* 10.1073/pnas.0803081105

- I find it rather easy to get close contact with other people.  
 I like it when other people are dependent on me.  
 I seldom worry about being abandoned by other people.  
 I don't like it when I have to be dependent on other people.  
 I don't like when other people come too close to me.  
 I feel ill at ease when I'm too close to other people.  
 I find it difficult to trust other people completely.  
 I feel anxious when someone gets to close.  
 I often desire more closeness and intimacy than others.  
 The thought of being abandoned rarely crosses my mind.  
 Have you discussed a divorce or separation with a close friend?  
 You and your partner are involved in common interests outside the family.  
 You and your partner have a stimulating exchange of thoughts.  
 You and your partner calmly discuss something.  
 Have you ever regretted getting married /moving in?  
 Do you kiss your partner?  
 Which of the following statements best describes how you feel about the future of your relationship?  
 5 I want desperately for my relationship to succeed, and would go to almost any length to see that it does.  
 4 I want very much for my relationship to succeed, and will do all I can to see that it does.  
 3 I want very much for my relationship to succeed, and will do my fair share to see that it does.  
 2 It would be nice if my relationship succeeded, but I can't do much more than I am doing now to help it succeed.  
 1 It would be nice if it succeeded, but I refuse to do any more than I am doing now to keep the relationship going.  
 0 My relationship can never succeed, and there is no more that I can do to keep the relationship going.  
 The dots on the following line represent different degrees of happiness in your relationship. The middle point, —happy,— Represents the degree of happiness of most relationships. Please circle the dot which best describes the degree of happiness, all things considered, of your relationship.  
 1 Extremely unhappy  
 2 Fairly unhappy  
 3 A little unhappy  
 4 Happy  
 5 Very happy  
 6 Extremely happy  
 7 Perfect