In Search of An Aphrodisiac

One of the most depressing facts of life is the progressive decline in sex drive and sexual responsiveness caused by the aging process.

Since the beginning of time, aging men and women have searched for an aphrodisiac to boost their flagging sexual potency. Among the many potions tried as sex stimulants have been Spanish Fly, raw oysters, ginseng, marijuana, cocaine, testicle transplants, and young sex partners.

Today—through the efforts of pioneering scientists—we are finally in the process of developing therapies with powerful aphrodisiac properties...drugs that can recharge our sexual batteries in remarkable fashion by acting upon the most important of our sex organs—the brain.

ANTI-AGING NEWS will report on the latest biochemical methods of stimulating sexual function on an ongoing basis. This is the first of these reports.

In 1970, W.E. O'Malley of Georgetown University startled his colleagues at a scientific meeting by reporting dramatic aphrodisiac effects in patients receiving L-Dopa therapy for Parkinson's Disease. He revealed that men in their 60s and 70s, who had been sexually inactive for years, had suddenly begun to make bold sexual advances to nurses and female patients—in some cases actually chasing them around the hospital with an amorous glint in

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their eyes.

O'Malley's report stirred considerable interest in the possibility of using L-Dopa as an aphrodisiac. It soon became apparent that his experience with the drug was by no means an isolated incident. Other investigators began to report extraordinary aphrodisiac effects in a significant number of their L-Dopa patients — women as well as men. A look at previous reports on L-Dopa revealed that sexual stimulation had consistently been observed as a side effect of the drug ever since it had been introduced into clinical medicine in the 1960s.

Downplaying L-Dopa's Aphrodisiac Effect

In large-scale studies of L-Dopa therapy for Parkinsonism, increased sexual interest and/or activity had been reported in approximately 4% of patients. In most cases, the aphrodisiac effect of L-Dopa was downplayed, and there was little or no speculation about its potential as a sex stimulant. In fact, investigators suggested that the increased sexual activity observed in Parkinson's Disease patients was due strictly to their improved general condition, not a specific aphrodisiac effect.

The practice of downplaying or ignoring the potential of L-Dopa as an aphrodisiac continues today. Few researchers even mention its ability to boost sexual function, although this effect has now been documented thoroughly in many clinics in the U.S. and Europe. Even the press, which turned O'Malley's findings into sensational headlines in 1970—seems to have forgotten about L-Dopa's possibility as an aphrodisiac.

A Pattern of Aphrodisiac Effect

Despite this neglect, a pattern of aphrodisiac effect has emerged from studies of L-Dopa over the past 15 years. Close inspection of the data reveals the following:

In studies in which the subjects were not questioned about their sexual habits, increased sexual interest and/or activity has been found in about 4% of cases.

In studies in which the subjects were questioned about their sexual habits, increased sexual interest and/or activity has been found in about 30% of cases.

Increased sexual interest and/or activity has been found in three times as many men as women. Analysis of the data according to sex shows that L-Dopa has produced an aphrodisiac effect in more than 50% of male Parkinson's Disease patients.

Role of Dopamine and Serotonin in Male Sexual Behavior

L-Dopa produces an aphrodisiac effect because it is converted in the brain into the neurotransmitter dopamine—one of several key chemicals that facilitate communication among neurons. L-Dopa or levodopa (L,3,4-dehydroxyphenylalanine) is a naturally occuring amino acid that is transformed into dopamine in the presence of the enzyme dopa decarboxylase.

There is considerable experimental evidence that male sexual behavior is stimulated by treatments that elevate brain levels of dopamine-hence the aphrodisiac effect of L-Dopa.

There is also considerable evidence that treatments that decrease brain serotonin also stimulate male sexual behavior. Serotonin (5-hydroxytryptamine—5HT) is another important neurotransmitter that is manufactured from the amino acid tryptophan.

G.L. Gessa and A. Tagliamonte of the University of Cagliari in Italy—who have studied sexual function in rats extensively—believe that male sexual behavior is"reciprocally controlled by a central serotonergic inhibitory and dopaminergic stimulatory mechanism." They feel that alterations in the ratio of dopamine to serotonin in the brain can markedly affect sexual function in males.

Animal Studies

There have been many studies in which manipulation of these neurotransmitters has increased sexual function in animals. For example, the injection of 5,6-dihydroxytryptamine (5,6-DHT)—which selectively destroys serotonin neurons—into the brain of male rats, significantly increases the percentage of animals reaching ejaculation when exposed for the first time to a female in estrus. In contrast, the administration of L-5-hydroxytryptophan (5-HTP)—the direct precursor of serotonin-suppresses male sexual behavior by raising the level of brain serotonin.

One of the most effective ways of decreasing brain serotonin is with the drug parachlorophenylalanine (PCPA), which is a

potent inhibitor of tryptophan hydroxylase—a key enzyme involved in the production of serotonin. PCPA has been shown to increase sexual activity dramatically in male rats.

A Spectacular Orgy

In one experiment, a combination of PCPA and pargylene produced extraordinary sexual behavior in male rats. The scientists watched in awe as males exposed to receptive females turned into perpetual sex machines. Hour after hour the animals engaged in a spectacular orgy. When a female wasn't immediately available, the supercharged males would feverishly mount each other, or anything that resembled another rat. The orgy climaxed with all the animals frantically trying to mount each other at the same time. It finally ended when the animals collapsed out of exhaustion.

Pargylene is a drug that inhibits monoamine oxidase (MAO), an enzyme that acts to break down catecholamines, including dopamine. By inhibiting the action of MAO, pargylene increases the amount of dopamine in the brain. When combined with PCPA, which depletes brain serotonin, it is capable of unleashing an unparalleled frenzy of sexual activity in male rats.

Similar effects have been produced in male mice, male and female cats, and female monkeys. Sexual stimulation has also been generated in animals by a combination of PCPA and the male sex hormone testosterone, which plays an important role in producing sex drive in both males and females.

Increasing Brain Dopamine Levels

When scientists used L-Dopa to increase brain dopamine levels in male rats, they were able to increase sexual activity slightly. But they were especially successful when they combined L-Dopa with RO4-4602 in animals pretreated with PCPA. This regimen markedly increased the number of animals reaching ejaculation.

RO4-4602 is a drug that inhibits dopa decarboxylase—thus blocking the conversion of L-Dopa to dopamine, but does not cross the blood brain barrier. The result is selective accumulation of brain dopamine. It also is somewhat effective in reducing serotonin levels. Dopa decarboxylase inhibitors are now given routinely in combination with L-Dopa in treating Parkinson's Disease patients.

Other treatments that increase brain dopamine levels have also been shown to spur sexual activity in rats. The drug apomorphine, which stimulates the dopamine receptors on brain cells, markedly increased mounting, intromission, and ejaculation in rats in doses as low as 30 micrograms/kilogram. However, high doses of apomorphine were ineffective in promoting sexual activity. Apomorphine also produces an aphrodisiac effect when combined with testosterone.

On the other hand, haloperidol—a drug that inhibits central dopamine receptors—suppresses sexual activity in highly vigorous copulators. A suppressive effect is also produced by pimozide--a centrally-acting dopamine antagonist.

Human Clinical Trails

Despite the wealth of evidence that drug manipulation of the dopaminergic and serotonergic systems can stimulate sexual interest and activity, there have been few clinical trials to test such drugs.

Angrist and Gershon of New York University gave high doses of L-Dopa (up to 6 grams/day) to two groups of psychiatric patients: ten suffering from schizophrenia, and six from other disorders.

Aphrodisiac effects were reported in 4 of the 10 schizophrenics. Two male patients had sexual delusions that were heightened when they received L-Dopa. One claimed he had been made impotent by a rectal examination performed by a physician during adolescence. The other complained of disturbances of the spine, which he felt had been caused by attempts at autofellatio (oral stimulation of his own penis).

One female patient displayed a dose-related increase in agitation caused by her belief that male patients were making sexual advances towards her. Another female patient, who had been preoccupied with sex in the past, became "spectacularly" seductive and hypersexual on L-Dopa. At a dose of 5 grams/day she stripped, ripped her pajamas bizarrely, and attempted to seduce any man she came close to.

Aphrodisiac effects were observed in 3 of the 6 males in the non-schizophrenic group. One experienced a significant increase in erections, often at unexpected times, such as while playing ping-pong with a nurse. Another

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reported a return of erections after several years of sexual impotence. The third, a 26-year-old homosexual, began masturbating at the rate of 4 to 5 times daily instead of his usual 4 to 5 times a week.

PCPA Therapy

O. Benkert of the University of Munich in Germany gave PCPA at a dosage of 1 gram/ day for 4 to 6 weeks to impotent subjects, and found that the drug had little or no aphrodisiac effect compared to placebo. Benkert feels that a higher dosage of PCPA might be more effective in recharging sexual appetites, but has yet to test this hypothesis because of PCPA's side effects, which include mental dullness, headache, and vertigo.

In an effort to improve the sexual function of headache suffers, Federigo Sicuteri of the University of Florence in Italy gave 16 male patients (age 40 to 65) a daily dose of 15 milligrams/kilogram of PCPA (orally) and 350 micrograms of testosterone (injected intramuscularly). He found that PCPA plus testosterone "provoked a highly significant increase in number of erections (usually at night)...with a lively accompaniment of sexual fantasy" when compared to PCPA and placebo or placebo alone.

In 11 of the patients, there was a return to normal sexual activity and a "striking" improvement in their psychological condition. They appeared "more lively, sociable, and younger." In six of the patients the aphrodisiac effect continued for several months after cessation of treatment because of unpleasant side effects.

Limitations of Studies

The clinical studies conducted to date have been inadequate in many ways:

1. Most studies have not been designed to test for aphrodisiac effects, but have looked for such effects in patients under treatment for Parkinsonism. The purpose of these studies has been to develop an effective protocol for Parkinson's Disease, not an effective aphrodisiac.

2. The few studies designed to test for aphrodisiac effects have been conducted in subjects suffering from impotence or in psychiatric patients. Impotence may be caused by psychologic or physiologic factors that cannot be reversed by drugs that may nevertheless be effective in normal persons. It may be that drugs which stimulate the brain's sexual control mechanisms are most effective in reversing the normal decline in sexual function caused by the aging process.

3. The aphrodisiac studies to date have been too small. Only large-scale, controlled studies in various types of subjects can determine the value of a therapy.

4. There are many drugs that affect the brain's sex centers. Up to now we've explored only a few possible aphrodisiac therapies. By testing various combinations of dopamine agonists, dopa decarboxylase inhibitors, serotonin antagonists, and monoamine oxidase inhibitors, we could develop safe and effective aphrodisiacs from currently available drugs.

5. Another way of developing such therapies would be to synthesize analogs of existing drugs that retain or increase their potency, while minimizing their side effects. The drug PCPA, for example, has considerable potential as an aphrodisiac, but produces undesirable side effects. An appropriate analog of PCPA might be a highly effective aphrodisiac.

6. Further study of how the brain controls sexual function will lead to additional approaches to the development of aphrodisiacs. As we learn more about how the brain controls sexual expression, we will develop new methods of increasing sexual interest and pleasure. One alternative to pharmacologic intervention, for example, is electrical stimulation of the brain (ESB)—a technique that has already been used to produce extremely pleasurable feelings in both animals and humans.

Research Possibilities

Among the research possibilities that should be explored further in the search for safe and effective aphrodisiacs are the following:

1. L-Dopa plus dopa decarboxylase inhibitors. Such combinations have proved more effective as aphrodisiacs in animals than L-Dopa alone, and are currently the treatment of choice for Parkinson's Disease. The two most commonly used dopa decarboxylase inhibitors are carbidopa and benserazide.

2. Other dopamine agonists such as apomorphine and a group of compounds called ergot alkaloids. One of these compounds—bromocriptine—is used to treat Parkinson's Disease.

Another—lergotrile mesylate—has extended the lifespan of laboratory rats. A third—Hydergine—is used to treat cognitive disorders in the elderly.

3. PCPA plus monoamine oxidase inhibitors. The addition of pargylene to PCPA caused profound aphrodisiac effects in rats. Another compound that may be a monoamine oxidase inhibitor is Gerovital-H3—which has enjoyed widespread clinical use as an anti-aging drug since the 1950s (see Jan. issue of ANTI-AGING NEWS, pg. 1-5).

4. L-Dopa (or other dopamine agonists) plus PCPA (or other serotonin antagonists) plus various dopa decarboxylase or monoamine oxidase inhibitors. If simultaneous boosting of the dopaminergic system and inhibiting of the serotonergic system is the vital mechanism that powers sexual expression, then combinations of drugs that best accomplish this objective should produce the most profound aphrodisiac effect.

5. The combination of compounds that stimulate the sex centers of the brain with steroids such as testosterone that help to trigger sex drive. Such a combination (PCPA and testosterone) has proved to be the most effective aphrodisiac to date in humans.

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Can Sunlight Improve Sex?

Contrary to the advice of those dour dermatologists who warn of the harmful effects of the sun's rays, there may be some reason to get out there and bask in a bikini.

Harper's Bazaar reports that Dr. Joseph Meitas, a professor of physiology at Michigan State University found that exposure to sunlight results in higher hormone levels and enlarged sexual glands in both men and women.

And if that weren't enough reason to close up the parasol, Dr. Russell Reiter, a professor of anatomy at the University of Texas, says that darkness triggers production of melatonin, a substance that inhibits sexual desire. Sunlight, on the other hand, reduces melatonin production, resulting in increased libido and fertility.

Two researchers at the Sex Research Institute at Indiana University cite statistics which indicate that the rate of intercourse peaks during July, during the longest days of the year. □□

Wacky inventor makes love potion out of toenails!

A crackpot college professor claims to have concocted the world's most powerful love potion — using nothing but ground toenails, ginger root and apple cider!

"This is the greatest aphrodisiac known to man," slap-happy scientist Dieter Altmeppin told a conference of sex therapists in Bern, Switzerland.

"Two drinks of this will turn a pussycat into a sexual tiger — and turn a sexual tiger into Superman."

Dingbat Dieter says he created the potent concoction in his laboratory in Vienna, Austria — and discovered its awesome powers the same night.

"It works wonders," he insists. "And you don't have to take my word for it — you can ask my wife. She's been one happy lady since this stuff came along."

The fired-up inventor says he's tried his love cider on dozens of droopy volunteers and turned 90 percent of them into whoopee-making whizzes.

But after listening to the prof's presentation at the therapy conference, a roomful of doubting docs seemed convinced daffy Dieter has finally lost his marbles.

"This guy is obsessed with creating the magic elixir that will make all men sexual machines," Dr. David Mertz, a Swiss urologist, later told reporters. "And some of his potions have actually looked promising on paper.

"But one after another of them has proven a dismal flop in the bedroom.

"And I guess all that failure has finally driven him off the deep end, because ground toenails, ginger root and apple cider — that's the goofiest thing I've ever heard of."

— *JOE BERGER*

S.F. EXAMINER

More nerve cells in spine may make

By Keay Davidson
EXAMINER SCIENCE WRITER

UC-Berkeley scientists say men have more "spine" than women — in a purely biological sense, that is.

Based on autopsies of 17 people, UC-Berkeley researchers have found that men have far more nerve cells in a part of the spinal cord important for copulation.

Men have 25 percent more movement-controlling nerve cells, or neurons, in a part of the spinal cord called Onuf's nucleus, say researchers Nancy G. Forger and S. Marc Breedlove in the October issue of the publication Proceedings of the National Academy of Sciences.

It's the third time scientists have found a basic structural difference between a man and a woman's central nervous system (CNS), which includes the brain and spinal cord, Breedlove said Friday.

Onuf's nucleus is located just behind the "small" of the back and below the ribs. It extends nerve channels to two muscles, the bulbocavernosus (BC) muscles and ischiocavernosus (IC) muscles.

In women, the BC muscle constricts the vaginal muscles and causes the clitoris to swell during intercourse. In men, the BC and IC muscles are used to urinate and to ejaculate semen, Breedlove said.

Their study focused on autopsies of eight women and nine men who had donated their bodies to science. The bodies are stored at the Armed Forces Institute of Pathology in Washington, D.C.

Forger and Breedlove found similar spinal differences between male and female beagles that had been killed for an unrelated research project, the article

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men better lovers

says. In male dogs, the relevant nerve cells were about 40 percent bigger than in females.

Their work sheds new but inconclusive light in a little-explored area: sex-related aspects of the nervous system.

Last year, researchers in Amsterdam said that a part of the brain linked to sexual behavior tends to be substantially larger in males than in females.

Other research, published in 1980, indicates that part of the corpus callosum — a bundle of fibers connecting the right and left halves of the brain — is larger in women than in men.

Scientists, including some feminists, have argued vehemently over the significance of alleged biological differences between men and women. Some researchers say sex hormones tend to spur emotional and intellectual differences between men and women, for instance, whereas critics say such differences tend to result from upbringing and social pressures.

Believers in male superiority have no reason to crow over Forger and Breed-

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love's work, Breedlove said.

Regarding the two previous reports of sexual differences in the nervous system, Breedlove said, "There's still a question whether those (differences) are biological in origin or due to different (life) experience. Second, their function remains unknown.

"Some people might be tempted to think these (structural differences) are related to sex differences in the way people think. But there's just no evidence of that. We know too little about the brain to say."

Forger recently received her doctorate in endocrinology at UC-Berkeley. Breedlove is a member of the UC-Berkeley psychology department and Group in Endocrinology.

That chemistry in his kiss may be a chemical

Oakland Tribune
June 3 1984

By Maury M. Breecher

What's the attraction behind kissing? A New Mexico State University psychologist believes the secret attraction — at least for women — is that it allows them to get a deep, intoxicating whiff of pheromones, those chemical scents that play an important role in sexual attraction.

Victor Johnston, an associate professor of psychology, says the nose "knows," that is, it recognizes the pheromone scent of "love," even though women are consciously unaware of the odorous lure.

While the role pheromones play in the sexual attraction of animals and insects has been known and documented for years, the role of these chemical substances in human courtship has been suspected, but never proven. Now, however, Johnston has, for the first time, documented that humans are affected by pheromones. Johnston documented the real attraction of pheromones by tracking their effect on brain waves.

He devised an experiment in which reactions of volunteers could be measured while they were unaware of the presence of the pheromone. Six male and six female volunteers were shown a series of photos of attractive males and females. Electrodes were attached to measure their brain waves. A plastic tube was run under the nose of each volunteer. They were told the tube was to measure their breathing, but actually it carried the odor of alcohol or, masked by the alcohol, very low concentrations of the pheromone Androstenol, a musky-smelling steroid which is secreted by glands under the roots of hair.

The subjects were asked to look at the photos. As they looked at the photos of the attractive men and women, Johnston measured the subjects' brain-wave activity while they were under the influence of the pheromone and while not under its influence. He looked at a particular brain wave — the P3 brain wave — which in earlier experiments had been found to reveal how much an individual liked or disliked a particular stimulus, such as a photo or a scene from a movie.

Without the added Androstenol, men had much larger P3 responses when they looked at photos of women — their P3 responses indicated they clearly preferred to look at photos of women rather than men. Women reacted about the same to photos of both sexes, but when the pheromone was added, the situation changed.

"My results startled me," Johnston said. "The responses of both males and females changed markedly under the influence of the pheromone. While males actually were less responsive when Androstenol was released, females became more selective. Females not exposed at all to Androstenol gave P3 brain waves the same size when they looked at both males and females. However, when the 'love scent' was released, they clearly preferred pictures of males.

"The P3 brain wave of men, on the other hand, dropped when they were under the influence of the pheromone. When they weren't under the influence of the pheromone, they showed increased P3 levels when they saw photos of attractive females. However, their P3 brain wave levels dropped when under the influence of Androstenol. This drop occurred when they looked at both male and female slides. However, they still reacted stronger to the female than to the male."

Johnston's findings that people respond sexually to odors — even if they aren't conscious of their response — suggest to him that body hair, particularly facial hair, has a previously unsuspected biological function.

For years, scientists have wondered why modern man still has zones of body hair. Johnston believes the answer is obvious — that hair "carries" Androstenol. As further support for the belief that hair has a biological function, he points out that the pheromone is produced at puberty, the same time coarse hair appears on the body.

Johnson believes that the act of kissing brings the female lovers' nose into close contact with her male lover's mustache and beard, allowing her nose to more easily whiff the pheromone. (The hair at the top of the head doesn't carry the pheromone. It has a totally different function — to keep the head cool and protect it from the sun.)

"I think we now have a better understanding of the biological function of hair and the reason why lovers kiss," Johnston said. "When a female kisses and is kissed, she is brought closer to the man's mustache and beard. The act of kissing seals her mouth and requires her to breath through her nose. Her nose detects the hair's pheromone. Since the act of kissing closes off the mouth, she has to breathe in through the nose, thus increasing the 'intoxicating' effects of the pheromone."

Why are we unaware of the pheromone's scent?

Johnston points out that the information

picked up by the nose doesn't get transmitted directly to the cortex, the part of the brain that makes logical decisions; but instead is fed into the limbic or "old brain" — the part of the brain which makes emotional decisions.

"The nose appears to be the meeting place between the chemistries of the sexes," Johnston says. "Silent chemical messages pass between us, expressing our inner desire and our readiness to respond."

Another expert, John Labows (Ph.D. in organic chemistry), a research scientist at the Monell Chemical Senses Research Center in Philadelphia — a non-profit research institute set up to investigate the senses of smell and taste — points out that it has long been known that pheronomes act as sexual attractors in insects and some lower animals, and it's long been suspected that they played some role in human sexual interactions. Speaking of Johnston's research, he said, "The research was innovative and imaginative. His research provides a tool to measure the effectiveness of these odors. He is using an objective measure of the effect of the odor rather than a subjective one. His research adds to the evidence that pheromones have a role in human sexual attraction."

"Sociobiologically speaking, this research is significant," said Robert A. Wallace, an adjunct professor of biology at the University of Florida and author of the books "The Genesis Factor" (William Morrow, 1979) and "How They Do It," a book on how animals mate (William Morrow, 1980). "From a biological standpoint, research of this type is becoming increasingly significant. There is a controversial area called sociobiology that states that a broad array of human social patterns are firmly grounded in biological principles. This is one more line of evidence that supports this position."

"When people are in love they often speak of an 'irresistible attraction' or desire to kiss, hug and touch the loved person. Johnston's research provides evidence that the attraction is a chemical signal designed by nature to attract women to certain men. Other pheromones, so far unidentified, probably also serve as sexual attractants," explained Wallace, author of several college textbooks, including "Biology, The World of Life" (third edition published in 1981 by Goodyear Publishing Co.).

"In fact," he continued, "in 1975, research at Emory University School of Medicine, revealed sexual attractants, which may be pheromones, in the vaginal secretion of human females. Concentrations closely correlated with their menstrual cycles — the research showed high concentrations of these substances when the woman was most fertile. Thus, it's logical to believe that these substances are there to aid in attracting men."

Body Odors

Amer. Health Dec. '83

It's Men . . . By a Nose!

If you cover your eyes and ears, can you tell who takes the seat next to you? Probably, says a team of scientists, you'll at least know whether your new neighbor is male or female. How? By your nose.

Like dogs, pigs and assorted other animals, people can sniff out the sex of their brethren. According to Dr. Richard Doty and his colleagues at the Monell Chemical Senses Center in Philadelphia, both men and women generally find men's odors more intense.

In studies of armpit and breath odors, both men and women told by a whiff which sex was which at a rate greater than chance, although women scored best. Still, there was a fair amount of guessing. If an odor was intense, it was likely to be thought male, whether or not its owner was a man or woman. Conversely, weaker odors were judged "female."

For the armpit study, participants used no deodorant, perfume, soap or shampoo for a week, although female "odor donors" shaved their armpits. They didn't bathe at all for 2[illegible] hours just before their armpits were sniffed. A T-shirt each had worn for a week was also sniffed.

To get their breath tested, subjects had their teeth cleaned professionally, then did not brush them again for five days. Hidden behind a curtain, they exhaled away as judges judged.

The reason men's odors are more intense, says Doty, is that men have far larger apocrine glands.

Located under the arm and in other hairy parts of the body, these sweat glands—turned on by sex hormones at puberty—produce a secretion that attracts bacteria. "By-products of the bacteria are what produce body odor," Doty notes.

Custom plays a role, too. Women traditionally shave under their arms: no hair, fewer bacteria to stay around, less intense odor.

What makes the difference in mouth odors is not clear, but Doty doesn't rule out hormonal differences having an effect there, too.

If men were to douse themselves with deodorant and mouthwash, would it make a difference? Yes, says Doty. But women might still find their smell unpleasant. Women are simply better smellers, and the stronger a smell, the less pleasant they judge it.

—Betsy Barley

SOME MEDICAL researchers contend that nitrous oxide, the laughing gas commonly used as an anesthetic by dentists, appears to be an aphrodisiac, at least for the female. Whether it also serves as a sexual stimulant for the male is not yet proved, they say.

Dopaminergic Drugs and Sexual Behavior

Psychiatric Capsule & Comment (Roche) Vol. 5 #8 Sept. '83

The role of dopamine-receptor antagonists in the development of impaired sexual function has been amply documented (see *Psychiatric Capsule & Comment*, February 1983). Reduced sexual drive and impotence are frequent side effects of such drugs, probably at least in part as a result of the increased prolactin blood levels caused by neutralization of the normal dopamine-induced inhibition of prolactin secretion (see *Psychiatric Capsule & Comment*, January 1983). On the other hand, ever since the introduciton of levodopa for the treatment of parkinsonism, there have been reports indicating that some patients experience a striking increase in libido, although some authors have at least suggested that this may have been "a return to normal" rather than a manifestation of "hypersexuality."

In Pursuit of Love: Three Current Studies

NY Times Jan 22 '80

By DAVA SOBEL

IT is superfluous to send chocolates to a loved one. Love is enough. Or rather, it produces the same response. Better to send chocolates to a rejected lover, since love lost may drain the body's store of a potent mood-altering chemical that chocolate has in rich supply.

In love, "chemistry" has always had a mystical connotation, but there is apparently a real laboratory-bench chemistry to love as well, involving compounds now being studied by Dr. Donald F. Klein and Dr. Michael R. Liebowitz at the New York State Psychiatric Institute.

Other current representatives of the scientific examination of love include research in Maryland to chart the brain pathways leading to romantic attachment, and confidential interviews by a psychologist in Connecticut who is attempting to establish a new definition of obsessional passion.

"Love brings on a giddy response comparable to an amphetamine high," Dr. Liebowitz said. "And the crash that follows breakup is much like amphetamine withdrawal." The reason for the similarity, he and Dr. Klein postulate, is that the loving brain pours out its own chemical correlate to amphetamine — phenylethylamine — while the spurned or disillusioned brain halts production of the substance and immediately begins to suffer from its absence.

While studying a group of "love junkies" with a life pattern of forming disastrous love relationships, Dr. Liebowitz noted that many of them went on chocolate binges when depressed. "Chocolate is loaded with phenylethylamine," he said. "The binging may be an attempt at self-medication."

Dr. Liebowitz's patients suffer extremes of elation and depression with a condition called "hysteroid dysphoria," which he compared to "living on a roller coaster." Most are attractive women, competent and likable, whose moods, self-esteem and ability to function at work or play are all determined by their love situation. He suspects that their levels of phenylethylamine fluctuate wildly because of an "unstable control mechanism" caused by an inherited or acquired defect, or possibly both.

"These women are in search of an emotional fix," Dr. Liebowitz said. "Yet they repeatedly foil themselves by picking inappropriate love objects — men who are married or too aloof to become involved in a lasting relationship. For a while the excitement stimulates them, but the man soon leaves, or is driven away by the constant, intrusive need for attention and praise."

By offering a combination of psychotherapy and drug treatment for this problem, Dr. Liebowitz has been able to observe patients' response to certain types of medications. When they are down they get no relief from mood elevators typically used to treat depression, while drugs that inhibit the breakdown of phenylethylamine lift their spirits and relieve the ur-

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gency to seek a "fix" in a new love object. Unfortunately, these drugs (called monoamine oxidase inhibitors) require a special diet (no red wine, aged cheese or other fermented foods) and can interfere with some women's ability to attain orgasm. Newer drugs, free of these drawbacks, may soon be available, Dr. Liebowitz said.

"Psychoanalytic treatment alone doesn't seem to be effective for these women because their overwhelming emotional states periodically wipe out the coping skills they learn in therapy," he added. "They need the drugs as well — at least for a while."

Dr. Liebowitz finds comfort in the biochemistry of psychic states, where the actions of chemical reagents replace the stigma of being "unlucky in love." Yet millions are affronted by scientific explanations in a realm where poetry reigns. Senator William Proxmire of Wisconsin, awarding one of his Golden Fleece awards to a psychologist whose research in love had been financed by the Federal Government, said, "I object to this not only because no one — not even the National Science Foundation — can argue that falling in love is a science. I'm also against it because I don't want an answer."

Defining Love Obsession

Partly as a result of this attitude, the scientific literature on love is relatively small, although love is a constant theme through the rest of literature.

Literary references appear frequently in the work of Dorothy Tennov, professor of psychology at the University of Bridgeport, who quoted Stendhal, Oscar Wilde and the letters of Héloïse and Abélard in her recent book, "Love and Limerence."

Dr. Tennov created the word "limerence" to denote a core of features particular to love obsession — preoccupation, acute longing, aggrandizement of the other's good qualities, see-saw ing buoyancy and aching in the chest — all perceived as intensely pleasure- or pain-filled, depending on the response of the "limerent object."

Although she claims to have made the word from pleasing sounds with no thought of etymology, limerence sounds as though it came from "limbic" — the part of the brain thought to control emotions and sexual behavior.

Unlike love, limerence is an all-or-nothing state, Dr. Tennov discovered in talking to hundreds of research subjects over 12 years.

"Nobody is ever just a little bit limerent," Dr. Tennov said in a telephone interview. "Nobody is limerent about more than one person at a time, and there is no such thing as bi-limerence." People may be heterosexual, homosexual or bisexual, she explained, but their "limerent objects" are all of one sex. Dr. Tennov hopes her new word will enjoy wide use, since it is a needed term distinct from love or lust. To wit: Love has no aim, as such, but limerence is intent on reciprocation and lust on satisfaction. Moreover, a person can love several others, have sex with many, but feel limerent toward only one at a time.

John Money, professor of medical psychology and pediatrics at Johns Hopkins University School of Medicine, agrees with Dr. Tennov that love needs new terminology and much more study.

"Textbooks of psychiatry don't include a diagnosis of lovesickness," Dr. Money said. "The syndrome needs its own special category, because it usually gets diagnosed as depression and is then treated with the wrong drugs. The surest prescription is to support lovesick people in therapy for the two years it may take them to recover. They'll know they're over it when they can have a new lover."

Dr. Money will discuss this and other findings in a book to be published in March called "Love and Love Sickness: The Science of Sex, Gender Difference and Pair Bonding."

Interested in the areas of the brain associated with love, Dr. Money has found that individuals who undergo surgery before or during their teens for the removal of pituitary tumors face lifelong difficulty falling in love.

"The surgery interrupts two sets of pathways that seem essential in erotosexual behavior," Dr. Money said. "One set tells the pituitary when to release hormones, and the other says when to get into appropriate mating behavior." Of the 27 tumor-surgery patients Dr. Money has followed with his colleague Richard Clopper, none has trouble making friends or establishing companionships, but only one has been able to form "a full-blown love affair."

How does true love smell?

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IT WAS A MYSTERY. The best looking, most mature girl in the class, Yolanda ("Yo-Yo") Braverman, was walking home after school every day with Dennis LeFleur, a kid nicknamed "The Flower" by his classmates. The mystery was because, apart from his other shortcomings, he had a body odor that hung over him like an invisible shroud.

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No one has ever established a clear connection between underarm odor and the attraction of the opposite sex. Still, there is an outside chance Dennis LeFleur may have had a treasure in those Gallic armpits. For the last decade the hunt has been on for links between the odor of bodily secretions and the mating process. Thus far no one has proven the existence in humans of such substances, called pheromones; in species of the insect world, such as bombykol-crazed male gypsy moths, these substances clearly direct behavior.

But the fragrance world took note a few years ago when British research chemist George Dodd isolated a steroid called alpha androstenol from male human sweat found in the armpits and genital area, and also found in larger quantities as a pheromone in the boar. In several tests, women were reported to have responded favorably to the substance, which is said to smell like sandalwood oil. They responded so favorably that they may have altered their behavior because of it.

In one test, British psychologist John Cowley had students wear masks impregnated with either androstenol or fatty acids. Then they were asked to assess job candidates. The womens' response was the most striking. Those wearing the androstenol masks favored the more assertive male candidates. Those wearing the fatty acid masks favored the more passive candidates.

Another experiment had students rate photographs of people before and after donning masks treated with androstenol. Both men and women considered the women in the photographs more sexually attractive while exposed to the androstenol. In still another experiment, androstenol sprayed on a traditionally avoided seat in a dentist's office attracted women and repelled men.

The results of these tests are far from conclusive in the eyes of some researchers. "There isn't any proven odor-mediated effect in humans as of now," said George Preti, a research chemist at the University of Pennsylvania's Monell Chemical Senses Center. "Few of those studies used control odors — another type of odor at the same level of concentration — to see if it would have mediated the same type of response."

Still, fragrance manufacturers, generous with their money in funding basic research — including Dodd's — were quick to jump on alpha androstenol. A British mail order firm marketed a perfumed spray version of alpha androstenol.

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Beyond the commercialization of alpha androstenol, researchers are working in other areas that indicate a link between bodily secretions and behavior. Thirty years ago French scientist J. LeMagnen found a link between the sex hormone level in women and their ability to detect exaltolide, a musky fragrance secreted in male urine. The ability to smell exaltolide, the scientist found, was greatest during the ovulatory phase of the menstrual cycle. He hypothesized that exaltolide, a primarily male odor that affects females, may have been a cue in early man for sex at a time when pregnancy was most likely.

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The Detection of 5α-Androst-16-en-3α-ol in Human Male Axillary Sweat

The 16-dehydro C_{19} steroid 5α-androsten-3α-ol (androstenol) is excreted in the urine of adult human males in substantial quantities (of the order of 1 mg/24 h urine) and in lesser amounts in adult female urine[1]. The physiological function, if any, of the 16-dehydro C_{19} steroids in man is unknown, but androstenol secreted in the saliva of the boar acts as a releaser sex pheromone in eliciting the characteristic immobilization response of the oestrous sow to the advances of its mate[2-4].

There are, however, circumstantial grounds for believing that pheromones may play a part in human behaviour[5,6]. Androstenol, which has a musk-like odour detectable by human subjects at extremely low levels (1–5 ng on water at 20 °C, 10 cm from the nose; BROOKSBANK, unpublished) is a likely candidate as a pheromone in man, though various other steroids can be smelt at much higher concentration[7]. External secretion, onto the skin surface, would be the most probable way in which human pheromones are exhibited. In view of the evident capacity of axillary glands and hairs for preferential uptake and release of steroids[8,9] and the similarity of axillary apocrine glands in morphology and in androgen-dependence to apocrine glands specialized in lower mammals for pheromone secretion[10-12], we believed that axillary sweat might contain sufficient quantities of 16-dehydro C_{19} steroids to be detectable by gas chromatography-mass spectrometry (GC/MS). Previous efforts, using GC alone

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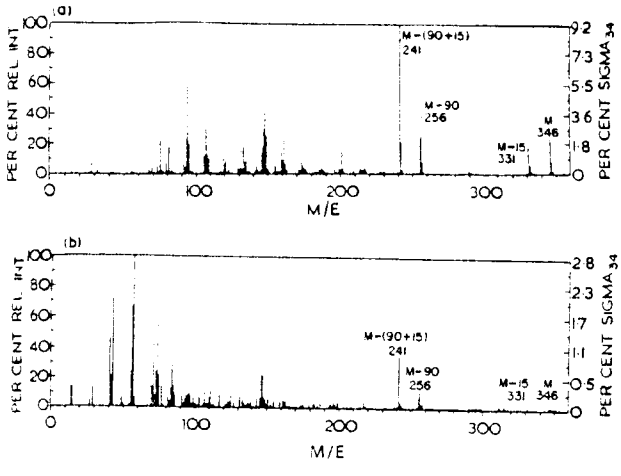
without internal checks on recovery (BROOKSBANK and CUNNINGHAM, unpublished), to detect these steroids in human axillary sweat had been unsuccessful, but GOWER and LLEWELLYN (see[4]) had detected 5α-androst-16-en-3-one (androstenone).

Axillary sweat was collected on defatted cotton-wool pads worn in the armpits by 12 healthy young men over a period of 5–7 days. The pads were exhaustively extracted with acetone followed by methanol, in the presence of a tracer quantity (2.4 ng) of 4,16-[7α-^{3}H] androstadien-3-one (androstadienone) (4.0 Ci/mmole). The soluble residue from the extractions was partitioned between water and benzene to furnish an oily extract ('sebum'[13]; 620 mg) containing unconjugated steroids, and an extract ('sulphated steroids') containing steroids excreted as sulphate conjugates that were recovered by acid solvolysis in ethyl acetate. The 'free steroid' fraction was redissolved in the minimum volume of hot methanol, and the material that precipitated on refrigeration overnight was removed; this cold methanol precipitation step was repeated. The methanol-soluble residue was taken up in benzene and free fatty acids were removed by washing the benzene solution with M.NaOH and with water. The neutral lipid material remaining, and the neutral extract obtained directly from solvolysis of the 'sulphated steroid' extract, were then separately chromatographed on alumina columns, additional tracers of [7α-^{3}H]androstenone (0.6 ng) and of [4-^{14}C]cholesterol being added at this stage. Fractions containing ^{3}H-androstenone, ^{3}H-androstadienone (marker for androstenol) and ^{14}C-cholesterol (marker for 5α-androst-16-en-3β-ol (3β-androstenol) were obtained by elution (cf.[4]) with light petroleum-benzene (9:1) followed by light petroleum-benzene (1:1). The column fractions were subjected to thin-layer chromatography (TLC) on silica gel in toluene-ethyl acetate (19:1 for the androstenone fraction; 9:1 for the other fractions).

Examination by GC on 3% QF-1 at 200° ('androstenone' fractions run underivatized, other fractions after reaction with chloromethyldimethylsilyl (CMDMS) ether reagent[14]) of the fractions recovered from the TLC plates showed that some androstenone might be present in the 'free steroid' extract but that further purification of the androstenol and 3β-androstenol fractions was necessary. This was carried out on alumina columns after hydrolysis of the CMDMS ethers (0.02 *M* HCl in 25% aqueous ethanol at 60° for 30 min), using the same solvent systems for elution as before. Analysis by GC on 3% QF-1 and 3% OV-1 columns at 195° and without formation of derivatives, showed that androstenol might be present in the appropriate fractions derived from the 'free steroid' extract. The small remainder of the purified fractions from the 'free steroid' and 'sulphate conjugate' extracts of sweat were therefore subjected to GC/MS, after reaction with trimethylsilyl (TMS) ether reagent, on a 1% SE-30 column incorporated in an LKB-9000 GC/MS system. Mass spectra, taken at 6 sec intervals, were analyzed in an IBM 1800 computer[15]. The presence of androstenol in the 'free steroid' extract of axillary sweat was shown by the occurrence in the 'androstenol' fraction of a peak with the relative retention time (t_R) (with respect to 5α-cholestane) of 5α-androst-16-en-3α-ol TMS ether (t_R = 0.16) with the fragmentation pattern characteristic of the authentic compound (Figure). No androstenol was detected in the corresponding fraction from the sweat 'sulphate conjugate' extract, nor was any androstenone detected in either extract.

The quantity of androstenol in the sweat 'free steroid' extract can only be estimated very roughly from the peak heights in the final GC chromatograms as no attempt at quantitative measurement was made. Allowing for the manipulation losses, assessed from the recovery of ^{3}H-androstadienone – which was not separated from androstenol except on GC –, there was about 4 μg of androstenol in the original 620 mg of sebum derived from the axillae of 12 adult men, that is from an area of approximately 300 cm² per day for about 6 days. Thus, androstenol, and probably also androstenone[4], do occur in axillary sweat from adult men. If they are significant as pheromones the excretion is almost certain to vary enormously between and within individuals and the amounts we have found are large enough to be consistent with a pheromonal function. However, the demonstration of a pheromonal function of any steroid in man remains to be made by other methods.



Mass spectra of authentic (a) and isolated (b) 5α-androst-16-en-3α-ol trimethylsilyl (TMS) ethers. The base peak in (b) (*m/e* 57) is formed from contaminating material with the same t_R as 5α-androst-16-en-3α-ol TMS ether; this explains the lower relative intensities of the peaks at *m/e* 346 (molecular ion, M), 331 (M–15), 256 (M–90) and 241 (M–(90 + 15)) in the mass spectrum of the isolated steroid when compared to that of the authentic compound.

Résumé. La présence du 5α-androstène-16-3α-ol d'odeur musquée dans la fraction contenant les stéroïdes libres de la sueur des aisselles, recueillie chez des hommes sains adultes, a été établie par chromatographie en gaz avec spectrométrie de masse. La quantité d'androsténol trouvée n'exclut pas la possibilité d'une fonction phéromonale de ce stéroïde.

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The secret of truffles: A steroidal pheromone?

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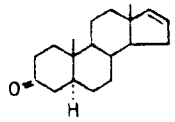
Summary. The steroid 5α-androst-16-en-3α-ol has a pronounced musk-like scent. It is a major constituent of the pheromone of the boar. It occurs also in axillary sweat of men but is devoid of androgenic activity. The presence of this steroid has been demonstrated in truffles (*Tuber melanosporum*) both by radioimmunoassay and by gas chromatography-mass spectrometry in quantities of 40-60 ng/g fresh material. This offers an explanation for the ability of pigs to detect truffles growing as deep as 1 m under ground.

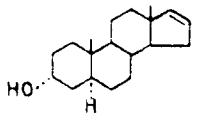
Some C_{19}-Δ16 steroids which have no androgenic activity exhibit a very peculiar smell[1-3] (fig.). The compounds are synthesized in the testes of the boar, are transfered to the salivary glands from which they are secreted during the premating behaviour. This scent, emanating from the saliva foam, is smelt by the sow and prompts her standing reflex. Thus Δ16-steroids, mainly 5α-androst-16-en-3α-ol are male sex pheromones in the pig[3,4]. Δ16-Steroids have also been detected in humans: 5α-androst-16-en-3-one and 5α-androst-16-en-3α-ol are synthesized by the testes and secreted with the axillary sweat in men[5-7]. 5α-Androst-16-en-3α-ol was found in the urine of women[8,9]. A possible pheromonal action of 5α-androst-16-en-3α-ol might be concluded from the studies of Kirk-Smith et al.[10]; judging the sexual attractiveness of photographs of normally dressed women the volunteers gave higher grades while smelling 5α-androst-16-en-3α-ol. The occurrence of Δ16-steroids is not confined to the animal kingdom. Celery and parsnip contain about 8 ng/g plant of 5α-androst-16-en-3-one[11]. Being aware of the ability of pigs to pinpoint the location of truffles (Tuber melanosporum), growing as deep as 1 m under ground, we extended our search for Δ16-steroids to this valuable fungus.

In a pilot study 1 g of canned truffles (from the Périgord, France) were homogenized in 3 ml of water and extracted with methylene chloride/ethylacetate (1/1). Aliquots of this crude extract were analyzed with our RIA system for 5α-androst-16-en-3-one, which cross-reacts with 5α-androst-16-en-3α-ol to 8%[12]. Further aliquots were subjected to TLC (silica gel, benzene/acetone = 85/15) in parallel to tritiated standards. After elution and subsequent radioimmunological measurement only 5α-androst-16-en-3α-ol but not 5α-androst-16-en-3-one was detected in a concentration (corrected for losses on TLC) which is in good agreement to the value of 25 ng/g measured in the crude extract (table).

For a 2nd study 4 g of fresh white truffles (Italian origin, purchased in a gourmet restaurant) and 4 g of black truffles from the Périgord (kindly provided by Mr Flourey) were homogenized and extracted. Measurement by RIA was carried out after isolation of the 5α-androst-16-en-3α-ol fraction on silica-gel (see table). The remaining extract was also purified by TLC after addition of ^{3}H-5α-androst-16-en-3α-ol as an internal standard. TMS derivatives were prepared and analyzed by GC-mass spectrometry as described elsewhere[13] (LKB 2091 instrument 1.5 m GC glass column with 1% OV 3 on chromosorb WHP) modified by a temperature program of 150–200 °C (3 °C/min). The identity with authentic 5α-androst-16-en-3α-ol was confirmed by gas-chromatographic retention time and mass spectrometric behaviour[3]. These data establish the presence of 5α-androst-16-en-3α-ol in truffles. The organoleptic examination of thin layer chromatograms of truffleextracts indicates that the fungus contains at least 1 additional musk compound of similar polarity, the flavour of which has a more herbal quality. Attempts for identification are in progress. It is remarkable that the concentration of 5α-androst-16-en-3α-ol in truffles surpasses its level in boar plasma 2-fold[14]. The biological role of this boar sex pheromone might explain the efficient interest of pigs in search of this delicacy.



5α-androst-16-en-3-one (urine smell).



5α-androst-16-en-3α-ol (musk smell).

Odoriferous Δ16-steroids.

5α-androst-16-en-3α-ol in truffles (ng/g): comparative measurements by RIA and GC-MS

Sample	RIA*	GC-MS
Canned truffles	26.3	–
Fresh black truffles	59.0	42.1
Fresh white truffles	61.6	58.6

* Corrected for cross reactivity. All values corrected for procedural losses.

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HINDU APHRODISIACS WORK

NEW DELHI, INDIA—Doctors researching ancient Hindu medicine say they have stumbled onto a formula for effective aphrodisiacs that will soon be available in do-it-yourself kits for India's already prolific population.

Dr. Gurdip Singh of the Gujarat Ayurvedic (Ancient Hindu Medicine) University said recently that the research was going to explode the myth that aphrodisiacs are ineffective. "Aphrodisiacs do exist and some of them can be prepared at home and administered safely."

Although the researcher declined to disclose his secret formula, he said the do-it-yourself kits could soon be within the reach of India's 650 million people, who already constitute the world's second largest population after China.

In ancient India, he said, aphrodisiacs were used only by Hindu and Moslem monarchs because most potions were made from such exotic ingredients as crocodile eggs, elephant dung, burnt pearls, musk, gold dust and lizards' eyes. One ancient recipe called for the administration of a soup made from a black partridge fed with small doses of mercury for 21 days.

Moghul kings like Mohammad Khilji in the 17th century and the Nabob of Oudh in the 18th century kept their court physicians busy grinding burnt pearls for dishes and drinks to increase the sexual prowess of the monarchs.

The Nabob of Oudh boasted a harem housing 3,600 concubines, but Khilji holds the all-time record by creating a city of 15,000 women—all at his disposal.

A colleague of Singh's, Dr. Ramakant Pandey, said present-day India does not need aphrodisiacs. "We are still grappling with our runaway population and looking for effective contraceptives."

A CHEMICAL KEY TO SEXUALITY

A simple chemical in the brain may be a crucial key to human sexual activity.

The compound, known as LHRH, leads a double life; it governs both the body and the mind. In one biological role, it is the chemical signal that controls the body's sex hormones and sets the whole reproductive process in motion. But LHRH is also a brain peptide, one of a newly discovered group of chemicals that may be intimately involved in memory, emotion and the perception of pain. In animals—including, perhaps, the human animal—LHRH carries signals to those parts of the brain that trigger mating.

LHRH and chemically related drugs are already being tested as male and female contraceptives, as treatments for infertility and even as possible aphrodisiacs, useful in the treatment of impotence.

Until the 1950s, medical researchers had thought that the pituitary gland was the master regulator of sexual activity. The gland releases chemical signals to the reproductive organs, where they affect the production of sperm, eggs and sex hormones. But the pituitary turned out to have its own master: a nearby brain area called the hypothalamus. The hypothalamus releases LHRH to the pituitary; this stimulates it to secrete certain reproductive substances.

At first, LHRH looked like an ideal treatment for infertility; giving a patient the hormone, it seemed, should stimulate the pituitary to boost the reproductive system. The approach was logical, but it failed to give reliable results. So chemists developed modified versions of the hormone, called analogs, that were up to hundreds of times more powerful than natural LHRH. They hoped that these potent agents would prove to be effective fertility drugs. But the opposite happened: the new drugs turned out to be contraceptives. Apparently the chemical signal they give is so strong that the pituitary rebels. Rather than stimulating the reproductive system, the drugs partially shut it down in both sexes.

Researchers realized that LHRH could form the basis for the first unisex birth-control drugs: contraceptives that could work in men as well as women. They are finally finding ways to use LHRH as a fertility agent, too. Rather than bombarding the body with powerful LHRH analogs, they are giving small, carefully timed doses of the hormone in an effort to mimic its natural flow in the body as closely as possible.

Even more controversial than its contraceptive-fertility applications is the possibility that LHRH may lead to the first scientific aphrodisiac. The hormone and some related drugs have proved to be chemical turn-ons for several animal species. The physiologist Robert Moss, of Southwestern Medical School in Dallas, has shown that LHRH is concentrated in parts of the rat brain that govern sexual behavior, and that LHRH-derived drugs act on those brain areas to send the animals into a mating pattern. The Chinese have used LHRH analogs to encourage carp to spawn and have used them experimentally in breeding pandas.

But will these drugs work for people? At present, no one knows. The human sex drive is complex, and a simple shot of LHRH or any other single chemical is not likely to be a complete aphrodisiac. LHRH must work together with other hormones to stimulate sexual areas of the brain. It is clear that the brain and body are intertwined, as Moss says, in "a very closely knit, tight package."

cool environment, they would choose the hot one. And these creatures had better survival rates than those given no opportunity to move to a hotter location.

The reason, he suggests, is that higher temperatures may destroy or deactivate the bacteria or perhaps have some beneficial effect on the body's disease defenses.

Pill Substitute

Rock Strap Birth Control

After working on the Pill for women, Dr. John Rock and a colleague, Dr. Derek Robinson, tested both the hot bath and a "scrotal muff" to suppress male fertility. Rock's insulated underwear drove sperm counts down dramatically for weeks. Wives of test subjects later had normal pregnancies.

So Rock argued that "a simple modification in modern clothing may provide a burgeoning population with an easy method of fertility control." Feminists suspect that if the Rock Strap had been for women, it would have been as widely ac-

ican Health November/December '83

claimed as the Rock Pill.

Indeed, the use of heat for fertility control goes back to the time of Hippocrates. And in the 1920s a Swiss doctor, Martha Voegli, completed 20 years of experiments in India using 116° F. baths. Men who could sit through the 45-minutes-a-day scald for three weeks, she reported, could count on six months of sterility.

People distrust the warming way to contraception, partly because it is not completely predictable. But for a family that wants to reduce the number of conceptions, it may be prudent and pleasant to get warm before getting physical.

Male Infertility

Cooler Cures

Sperm thrive on Blue Ice

To help an infertile man, urologists tend first to worry about temperature. Above 95° F., live-sperm count often runs low, and for some men Mother Nature's special cooler, the scrotal sac, is not cold enough. Now it seems that a cold shower might help.

The idea isn't new. In 1968 Dr. John Rock, co-inventor of the Pill, prescribed swimming in cold water as a means of increasing fertility. The idea submerged during the water-bed era, but now it's back in the form of new portable coolers:

■ THD, Testicular Hypothermia Device. Dr. Adrian Zorgniotti (212-249-3064), head of urology at Cabrini Medical Center in New York City, keeps a scrotum covering cool by constant drips from a water pack. After the husbands in 26 "hopeless couples" wore the THD for an average of 14 weeks, 10 of the wives became pregnant. Still in FDA tests, it will cost $300 to $400.

■ Male Virility Device, an athletic supporter holding a flexible pack of Blue Ice like that used in picnic coolers. Invented by Oceanside, CA, chiropractor William Kupferer (619-757-1919), who also boasts that it brings "increased sex drive and potency," the MVD sells for $39.95. Mainstream researchers have no evidence that cooling boosts sex drive.

■ Homemade Picnic Pack. At Indiana University School of Medicine (317-630-6229), urologist John J. Mulcahy showed 50 infertile men how to fit $1 worth of Blue Ice from local department stores into jockey shorts. In a couple of months, two-thirds of the men doubled or tripled their sperm counts.

■ Hot-Tub Ban. After California and Oregon urologists found frequent infertility among hot-tub users, word spread about its side effects. Orthodox Jews who take hot Mikvahs (holy baths originally intended for women) have also been alerted to the benefits of cooler water.

—*Carol Tavris*

BREAKTHROUGH CAPSULES Potency restored -- New method of treating organic impotence with drugs instead of surgically implanted devices. User injects mixture of blood vessel-dilating drugs into the base of the penis 20 minutes before coitus -- resulting tumescence lasts about three hours. Early studies extremely promising: 29 of 31 impotent men achieved intercourse via the new treatment. Pioneer: Dr. Adrian W. Zorgniotti, professor of clinical urology, New York University, 70 Washington Square S., New York 10012 ..... [illegible] $60 million

BOARDROOM Reports MARCH '85

Impotence cured electronically

Impotent men may soon be able to reverse their problem at the push of a button, thanks to a collaboration between medicine and electronics.

Last year, in several laboratories around the country, scientists discovered a group of nerves in the groin that seems to control erections. Already, a Philadelphia company, Biosonics, Inc., has developed a device called the Male Electronic Genital Stimulator, or MEGS, that can be hidden in the rectum and, by remote control, stimulate the vital nerves. Monkeys wearing it have maintained erections for nearly an hour and a half, says inventor Henry Brenman of Philadelphia's Jefferson Medical College. No test, however, has determined whether ejaculation terminates a MEGS-induced erection.

MEGS is not yet available. FDA approval is pending, and Biosonics says the stimulator will be sold only by prescription from a physician. ■

RELAXIN SPEEDS SPERM

Sci. Digest Nov 84

Relaxin, a hormone discovered in 1926 in female rodents, has now been shown to improve the performance of human sperm. According to Gerson Weiss, a New York University endocrinologist, relaxin, which is made by the prostate gland, increases sperm's motility. Treated sperm placed in cervical mucus traveled farther than sperm without the hormone.

FDA panel urges halt to love potion claims

WASHINGTON (AP) — Spanish fly and other folklore-celebrated love potions are unlikely to have the aphrodisiac powers claimed for them in advertising, according to a Food and Drug Administraion scientific panel.

The advisory panel's findings, published in the Federal Register, dealt with oral drugs containing cantharides — Spanish fly, made from dried beetles — as well as ginseng root, licorice, sarsaparilla, pega palo leaves, nux vomica, yohimbine, gotu kola and don qual.

These drugs, the panel recommended to the FDA, should not make claims like "acts as an aphrodisiac," "arouses or increases sexual desire and improves sexual performance," "builds virility and sexual potency" or "expands the gift of love."

"Such claims have i mitted largely throu and exploited by ma who prey on the g people who are mos need of counsel or the experts said.

In another notice ap the Federal Register, a FDA scientific advisor took issue with Alka-S claim of "speedy relief"

Drug for addicts invigorates mice

H CHRON 5/1/82

PHILADELPHIA (AP) — A drug that helps humans overcome morphine addiction kept laboratory mice slim and hungry for sex, a Temple University researcher says.

Mice and rats fed a diet of M&M candies, chocolate-chip cookies and ice cream grew to the rodent-weight equivalent of an 800-pound human if they were deprived of the drug, but they remained fit and vigorous if they took the drug at the same time, said psychology professor David L. Margules.

The drug also awakened dormant sex drives in mice and rats, causing some animals which previously had shown no interest in sex to "copulate intensely," he said.

The experiments were conducted recently by researchers at Temple testing the properties of naloxone, manufactured by Dupont.

"We've tracked it over a period of several months and it looks quite effective," Margules said Thursday. "It is beneficial to weight loss, increased energy expenditure and increase of libido."

Margules said the drug works by blocking receptors in the body that absorb chemicals called endorphin and enkephalin produced in the brain and the pituitary gland.

Morphine has a chemistry similar to that of the body chemicals so the drug helps curb addiction by blocking the absorption of the opiate pain-killer, Margules said.

The two body chemicals affected by the drug have a depressant effect on the reproductive and respiratory systems while at the same time they tend to increase appetite, Margules said.

"They inhibit the libido, cause constipation and slow down respiration," Margules said, describing the chemicals' function.

"It is a system that allows us to conserve energy," he said. "It is a system that allows us to act like animals in hibernation."

Conservation is fine at times of famine, but when there is an abundance of M&M's, cookies and ice cream around, humans can become as fat as rats if the two chemicals get out of whack, Margules said.

Naloxone, by blocking the receptors from absorbing the body chemicals, frees those parts of the body which are affected by the chemicals and speeds up the metabolism, he said.

Margules said he foresaw possible widespread use for naloxone in sex and diet therapy, but he cautioned that not all the drug's properties have been tested.

He said some of the receptors blocked by the drug are part of the body's immunity system which fights disease.

"Nothing comes without a price," Margules said. "Once we know how the immune system is influenced we might find out there are other risks."

LOVE'S SWEET TORMENT

Along with immortality, or at least eternal youth, humans have yearned through the centuries for a simple, effective aphrodisiac with which to stimulate desire, either in themselves or in the objects of their affection. Ancient herbals and other documents show that men and women have tried a variety of aphrodisiacs including powdered rhinoceros horn, nuts, truffles, even coffee—all with uncertain results.

Now scientists at the Salk Institute believe they have discovered a peptide molecule, a compound of amino acids, that has true aphrodisiac effects. The molecule, an analogue of peptide substances that are also being studied as possible contraceptives, is now being tested on rats by Dr. Robert L. Moss at the Southwestern Medical School in Dallas, Texas. Dr. Moss has reported that in preliminary experiments the substance has not yet failed to stimulate sexual activity in these happy animals.

The aphrodisiac peptide is a chemical cousin of a naturally occurring substance, the luteinizing hormone releasing factor. That substance is produced in the hypothalamus to act upon the pituitary gland, causing the pituitary in turn to release a luteinizing hormone. This is carried by the bloodstream to the female ovaries, where it triggers reproductive activity, and to the male testes, where it causes increased production of testosterone.

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WOMEN IN LOVE

Having tasted both sides of sex, the ancient sage/sex-changeling Tiresias (famous for his dire warnings to Oedipus) pronounced that sex was more fun as a woman. Three millennia later brain researchers may be discovering why.

For men, sex is reflexive, a psychomotor activity, says neuropsychologist James W. Prescott, of the Institute of Humanistic Science, in West Bethesda, Maryland.

Studies show that when the neurotransmitter dopamine, necessary to psychomotor activities, sinks to pathologically low levels (as in Parkinson's disease), sex is curtailed in men, but not in women. Thus, researchers speculate that female sexual behavior is regulated by different neural pathways.

Psychomotor activity tends to be focused and goal oriented. Women's brains, less "focused" during sex, are better equipped to luxuriate in its emotional and spiritual dimensions, according to Prescott.

Female accounts of orgasm often describe sensations characteristic of altered states of consciousness: floating, loss of body awareness, a sense of unity with the partner. Prescott believes the vestibular-cerebellar system, a part of the brain governing balance, touch, and movement, may account for these phenomena.

Female chauvinists, take note: According to Prescott, the human female is distinct from her mammalian sisters in experiencing sexual desire independently of estrus. Thus, for women, sex has a purpose beyond reproduction. Men's sexual makeup, conversely, represents no dramatic departure from that of lower mammals.

"All this is just speculation at this point," says a more cautious brain researcher, Jaak Panksepp, of Bowling Green State University, Ohio. "The only hard data are the studies with dopamine."

Panksepp's work with rats links dopamine with psychomotor stimulations. Rats with high dopamine levels ran around more, "self-stimulated" (pressed levers for rewards) more, ate more, responded more to the environment, and generally were more "outward directed." Interestingly, women generally register lower dopamine levels than men do. —J.H.

Hormones

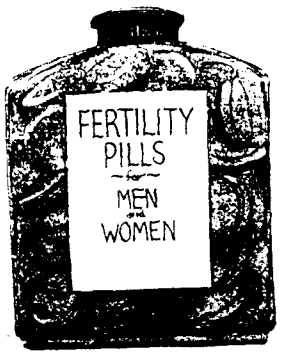
Fertility Pills for the Brain

They're "hot." They're also three years or more away, so don't rush out for a prescription. That's the advice about the oncoming generation of hormonal birth control pills.

The sizzle in the pills is their potential. Because they involve sex and the brain, they are among the most exciting biological substances to seize the attention of modern medicine.

The new compounds are chemical cousins, all variants of the brain's master fertility control, luteinizing hormone releasing hormone (LHRH). Early clinical tests show that one or another of the LHRH analogues can do what no other substance has yet been able to do: suppress fertility effectively and safely in men as well as women, and serve as a morning-after "pill" and a conventional "pill" all rolled into one.

At the current rate of progress, the first LHRH contraceptive for women is at least three to four years away. The one for men is further down the pharmaceutical pike.



What has scientists most excited is the versatility of the analogues. Given at one time, they actually stimulate reproduction in infertile men and women. Given at other times in other doses, they become birth control agents, interrupting the complex brain-body signals that underlie reproduction. Given to children, they correct the pathologically early hormonal awakening that causes precocious puberty. They are also used to treat prostate cancer.

"These are far more interesting substances than the earlier birth control agents, the steroids," says Gabriel Bialy, Ph.D., head of contraceptive development for the National Institutes of Health. "You can almost say they are the new toy on the market."

In a recent trial, an LHRH analogue developed at the Salk Institute in La Jolla, California, gave month-long protection against pregnancy to four of five women when injected for three days, beginning at the time of menstruation. Given at this time, even in tiny amounts, the brain hormone interferes with the normal reproductive process by making the uterus inhospitable for implantation of a fertilized egg.

Says Samuel S.C. Yen, M.D., the University of California at San Diego gynecologist who conducted the clinical trial: "It offers the possibility of a once-a-month Pill."

How to Score with Eau de Boar

LONDON—Behaviorists researching the subtle effects that odors exert on human behavior are getting a considerable experimental boost from traditional English swineherds and sex-shop proprietors. Not long ago, scientists at Warwick University isolated a hormone called alpha androstenol, produced by male swine and humans alike, that allegedly attracts females. Hardly had the first technical studies been published on this pheromone—a secretion that affects the behavior of other members of the same species—than pig farmers were volunteering whole herds as test subjects and cologne makers were competing for the patent.

To pig farms it's merchandized as Boarmate, and said to be notably efficacious. Like many domesticated livestock, sows frequently fail to "show" properly during their heat periods; their pudenda fail to swell and give off the aroma that attracts males. The boars in turn don't get aroused, and a valuable breeding period is lost. When the sows are exposed to Boarmate, though, at the proper time of the month, they luridly exhibit all the proper symptoms; the boars pick up on it, and everything works okay.

In humans it's a little trickier, since most women don't have regular and well-defined mating periods. However, one set of researchers tried daubing a minuscule trace of alpha androstenol onto a seat in a dentist's waiting room, and sure enough, every woman who came into the room headed straight for that particular seat—while men appeared to avoid it. When a trace of it was sprayed in a phone booth in a London railway station, men and women alike stayed inside it for a longer period of time than folks in other booths. Warwick researcher Dr. Michael Kirk-Smith exposed men and women to tiny, unnoticeable sniffs of the pheromone and had them look at pictures of women: both sexes reported that the women looked sexier and more attractive when they'd been exposed to alpha androstenol.

Still, scientists theorize that alpha androstenol, which is exuded in male sweat, tears and even earwax, should have a decidedly greater effect on women than on men. In sizable quantities it smells like sandalwood, but doses as low as a trillionth of a gram are supposedly sufficient to touch off the desired response—subtle arousal in women.

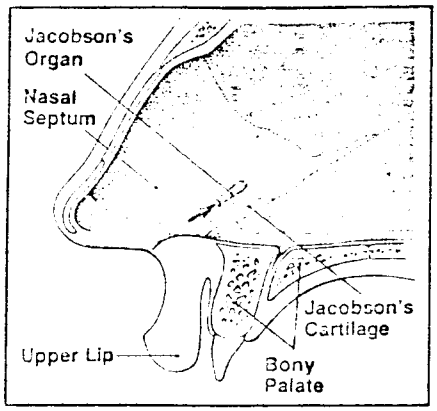
Accordingly, sex-shop owners here have lately begun to offer alpha androstenol under the brand name Aeolus 7. (Aeolus was the Greek god of the winds, for what that's worth.) It's peddled as a spray, or on a handkerchief lightly impregnated with it, and the scientific world is awaiting the results with bated breath.

Aeolus 7 may well, in fact, turn women on—and if so, what it may do to *men* is anybody's guess. Human pheromones are implicated in a wide variety of behavior, including dominance patterns. It's suspected that alpha androstenol may have a lot to do, for instance, with deciding which male monkey in a troop is top banana. A normally soft-spoken, mild-mannered gent who sprays some onto himself, then, might well gain an unconscious sense of unaccustomed self-confidence; and he might also touch off the instinctive, brutish hostility of all the men around him and wind up with a series of brawls on his hands.

ONE BEAUTIFUL ORGAN

In the nose of every mammal except the porpoise is Jacobson's organ, a small, obscure structure whose purpose has been disputed since the early nineteenth century. Some say it isn't worth arguing about, that it's just a vestige like the appendix. But at least one scientist says it may be a crucial factor in reproductive behavior.

This tiny organ is probably the sensory



One scientist believes this nasal organ is a crucial factor in reproductive behavior.

receptor for pheromones, the sexual scents that attract insects and animals and, doubtless, humans, says Dr. Charles Wysocki of Florida State University. He quotes the biologist V. E. Negus as saying this about it:

"The bilateral organ in question is so beautifully designed that one cannot fail to ascribe a purposive function to it. It seems incredible that a carefully arranged system of specialized epithelium, with its own nerve supply, with numerous glands emptying into it and with a duct communicating with the exterior by a more or less devious route, should not play some important part in the animal economy."

That purpose, Wysocki says, can be inferred from a variety of evidence. Jacobson's organ is quite independent of the main olfactory system, both anatomically and neurologically. The olfactory organ, which communicates such things as the aroma of pine forests or burning rubber, is connected to the thalamus and the telencephalic cortex. Jacobson's organ, on the other hand, has intimate nervous connections with the hypothalamus, which is the key regulator of hormonal and reproductive activities.

When Jacobson's organ is experimentally interfered with, reproductive behavior in animals is severely affected. Detrimental changes take place in all sorts of functions, including hormone secretion, female fertility, mating habits, mothering and even nest building.

And because scent reception plays such an important part in the time and frequency of reproduction and in the choice of a mate, it may exert a powerful influence on the genetic makeup of following generations.

Wysocki admits that some of the evidence is scanty and that no firm conclusions should be drawn without further study. But with so many experimental clues, and because of the almost universal existence of Jacobson's organ in mammals, it does seem to be the logical site of reproductive chemoreception.

The Sniff Test

You probably smell better than you think. At least that's what Richard Porter, a psychologist at Vanderbilt University in Nashville, Tenn., has found. Porter's been conducting tests to determine whether family members could identify each other just by the smell of their garments.

According to *Omni*, he gave 12 pairs of siblings white T-shirts, in which each child was to sleep for three nights.

Nineteen out of the 24 children were able to pick out the shirt worn by their brother or sister. In a similar test involving 18 parents, all but two could identify their child by his/her smell. In addition, after two days mothers of newborns could successfully complete the test.

Porter knows that this works; what he is still trying to figure out is whether this smell awareness is genetically coded or learned. □□

How male scents can improve women's lives

S.F. CHRON. NOV 18 '86

By Boyce Rensberger
The Washington Post

Scientists in Philadelphia have established for the first time that human beings produce pheromones, special aromatic chemical compounds produced by one individual that affect the sexual physiology of another.

Although animals have long been known to secrete pheromones, which typically function as sex attractants, and although the existence of such chemicals in humans has long been speculated, the new research is the first to establish their existence in humans.

The human pheromones are not sex attractants, nor do they act almost immediately as animal pheromones do. Instead, the human pheromones act over a period of weeks or months to alter the timing of women's menstrual cycles.

The discovery, by scientists at the Monell Chemical Senses Center and the University of Pennsylvania medical school, is believed to help explain a long series of puzzling findings — linking sexual behavior and the health of a woman's reproductive system — that the researchers have obtained in a landmark series of studies over 13 years.

In those studies it was found that women who have sex with men at least once a week are more likely to have normal-length menstrual cycles, fewer infertility problems and a milder menopause than women who are celibate or who have sex in a sporadic "feast-or-famine" pattern.

The pheromone findings indicate that an essential factor, aside from sexual intercourse itself, is exposure to

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Scents

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specific aromatic chemicals exuded in a man's normal body odors. When a woman receives these chemicals, by smell or skin absorption, even though she may not consciously notice them, they automatically improve her physiological functioning.

The evidence suggests that the male chemicals, which are secreted in special sweat glands in the armpits, and possibly also around the nipples and in the genital region, are not effectively transmitted except in the intimate contact ordinarily associated with sex.

Although the chemical nature of the substances is not yet fully understood, the scientists hope to create synthetic versions for various practical applications. Among the possibilities are nasal sprays to correct certain forms of infertility, to regularize the menstrual cycle, to make the rhythm method of birth control more reliable and to delay or ameliorate menopause.

The Philadelphia researchers have been able to duplicate some of the male pheromone's effects by exposing women who had no current sexual relationship to male pheromones in the form of what they dubbed "male essence." This contained substances extracted with alcohol from absorbent pads that male volunteers wore under their arms.

The study was done with female volunteers whose menstrual cycles were longer than 33 days or shorter than 26, deviations from the normal average of 29.5 days. Three times a week the women came to the clinic to have male essence rubbed under their noses. The women said they could smell only the alcohol.

After about 12 to 14 weeks, their menstrual cycles changed, slowing in some cases and speeding up in others, to approximate 29.5 days. A control group of similar women who were dosed only with plain alcohol showed no significant change in cycle length.

RELIEF IS JUST A SWALLOW AWAY

(CHIC JUNE '78)

Look out, America! Here comes the orgasm pill

By William Richman

Seventeen years ago, long before the advent of vibrators and life-sized rubber love-dolls, Tulane University psychologist Robert Heath conducted an unusual experiment in synthetic sexuality. Bypassing his female subject's body altogether, Heath concentrated instead on the specific area of the brain that takes its orders directly from the clitoris. He massaged that set of brain cells with an injection of a chemical called acetylcholine. *Within seconds, the woman registered a shattering orgasm.*

More recently, a team of neurologists at Ohio State University injected an unwieldy chemical called (d-Ala^2)-methionine-enkephalin directly into the brains of several hundred white rats. The most immediate result of the enkephalin injection was that the rats became torpid, much like little junkies nodding out in front of little television sets. But when the scientists took a closer look, they found that three out of four rats had left *telltale white puddles* in the bottoms of their test tubes. The rats, too, had achieved what amounted to a sexless orgasm.

As far as the researchers themselves are concerned, these results are simply curiosities. Neither Tulane's Heath nor the Ohio State neurologists think of themselves as the discoverers of the synthetic climax. Still, the question remains: If it can be done in the laboratory, *why not in the streets?* Can a science that gave us the hydrogen bomb and Alka-Seltzer provide us with speedy relief from sexual frustration via an orgasm pill?

The experimenters themselves think we should forget an Orgasil or a Cuminex and resign ourselves to the sweat and bother of the old rub-a-dub. Larry Stein, a brain researcher for Wyeth Laboratories in Philadelphia, maintains that no commercial pharmaceutical firm would be interested in producing an orgasm drug. Even if Stein is proved wrong — drug companies generally do not consult with their researchers before making marketing decisions — a come pill would probably be regulated even more severely than morphine, say, or nerve gas. It would likely be limited to such clinical applications as the curing of frigidity.

Of course, Albert Hoffman had no idea that his accidental discovery of LSD would provide a whole generation with a drugstore shortcut to the wisdom of the ages. The manufacture and distribution of LSD was almost wholly an underground affair, so why couldn't Orgasil or Cuminex go public in much the same way? Well, say the scientists, LSD can be made cheaply by any B+ chemistry student with access to a few ordinary compounds, whereas the synthesis of the chemicals used in sex experiments requires machinery so elaborate and techniques so sophisticated that basement manufacture is out of the question. And the production costs are so high — the substance used in the Ohio State experiment goes for about $300 a milligram, making it about 3,000 times as valuable as cocaine — that synthetic orgasms could never qualify as a cheap thrill.

But these pessimistic appraisals fail to take into account two important factors: Yankee ingenuity and society's present hunger for drugs in general. Imagine, for example, a lab technician at Lilly or Upjohn who is responsible for the actual manufacture of a substance like methionine-enkephalin. Realizing the potential of what he's doing, the technician devotes a year of night work, using the lab's equipment (technicians often work odd hours and usually have keys), to develop a drug that is safe, non-addictive, can be taken in tablet form and produces an almost instantaneous orgasm. He succeeds. He gives 100 tabs to his girlfriend, 50 of which mysteriously end up in the oversized hands of a second-string tight end for the New York Giants. (God knows the Giants need *something!*) The pills circulate through him to his teammates and to the team physician, then out into the greater society of athletes, entertainers and doctors. The lab technician opens up operations at home, using the proceeds from his first batches to buy a $200,000 synthesizer. Two years later he sells out to the Mafia, buys a Ferrari and begins to take lavish vacations.

Orgasil spreads. At first its uses are recreational and confined to individuals. The jaded carry tabs along to potentially boring parties. Those with short attention spans now have something better to do during commercials and the singing of the national anthem. Later, groups of friends and strangers galvanize around the instant orgasm as Cuminex parties become the rage in Mill Valley and Worchester County. At the Los Angeles Coliseum, 80,000 teenagers experience simultaneous climax at a Peter Frampton concert; the stadium has to be closed for repairs. The only groups to remain unaffected are politicians and astronauts, for whom the drug simply does not seem to work.

Society begins to feel the changes. Divorce rates stay about the same as some marriages are saved and others irredeemably split, but birth rates plummet. A serious literature emerges to praise the merits of Sex Without Contact. Sociologists report an increase in job satisfaction among employees of companies that provide Orgasil breaks, and a remarkable improvement in the stability and comportment of soldiers, prisoners, bus drivers and nuns. Venereal disease and mononucleosis become medical curiosities; impotence becomes irrelevant. Cuminex-treated rice is distributed throughout the Third World; in 1984 India reports only 14 births. At the other end of the spectrum, come pills now outrank sleeping pills and ledge-jumping as the preferred method of suicide.

Fragmentation sets in, to be followed by reaction and reform. Yogis, hypnotists and biofeedback experts deride the dependence on pills, eventually learning how to produce sexless, drugless orgasms by applying the power of positive thinking. (Their method takes a little longer, sometimes up to six weeks per climax, but gives a feeling of satisfaction unattainable with the drug.)

In the meantime, streetwalkers and call girls form an alliance with sexual fundamentalists. Together, they pressure Congress to pass anti-orgasm legislation. Laws that make it a misdemeanor to come in supermarkets, theaters and other public places are soon extended to include the privacy of one's bathroom. The movement dies out; the birth rate picks up again.

Some will say that such a scenario is about as unlikely as the development of the orgasm drug itself, that human psychology demands contact and some degree of emotion as precursors to lovemaking, and that biology is notorious for demanding children. These conservatives may argue that sex in the flesh is to the synthetic variety as eggs Benedict is to Instant Breakfast. Otherwise, those life-sized girlie dolls would be outselling prostitutes by two to one. Sex, the conservatives may say, is only one of a whole panoply of nifty experiences, and you may just as well manufacture a pill that recreates in its users the exhilaration of hang-gliding or the calm of a walk by the ocean.

More adventurous types wouldn't be in the least convinced by those arguments. Taking the attitude of engineers and nuclear scientists, they would say that if a thing *can* be done it *should* be done. For those people, and for others who, for whatever motive, maintain an interest in the possibility of synthetic orgasms, we present the recipe for (d-Ala^2)-methionine-enkephalin, the substance that did it for the Ohio State rats:

Basically, the trick is to replace the glycine that occupies position two in the amino acid chain that makes up methionine-enkephalin with a d-amino acid. To do this, use (and we quote) "solid-phase methods with t-butyloxycarbonyl protected amino acids. Those analogs with free carboxyl C-termini are assembled on a methionine-Merrifield resin. . . . The hydroxyl group of tyrosine is protected with the 2-bromo-carbobenzoxy group. The final Boc-group on the tyrosine residue is removed by acidolysis before hydrogen fluoride cleavage to avoid alkylation of methionine. . . . Free peptides are liberated by treatment with hydrogen fluoride/anisole and are readily purified by gel-filtration on Sephadex G-15 by elution with .2M acetic acid . . . followed by partition chromotography on Sephadex G-25, using the bi-phasic solvent system n-butanol:acetic acid:water (4:1:5)."

Caro Professore Aphrodisiaco:

Few scientists gain public notoriety by publishing a paper in the weekly journal *Science*. Stanford neuroendocrinologist Julian Davidson did. Which merely reaffirms the power of sex: Davidson's article

speculated about possible aphrodisiac qualities of a drug derived from the bark of an African tree.

Davidson hadn't counted on the instant furor over yohimbine hydrochloride. "My telephones at home and at work started ringing off the hook," he says. "Radio personalities, talk show hosts, and even rock-and-roll stations called me requesting live interviews."

Davidson was eager to cooperate, hoping an explanation of his research might encourage public awareness and serious discussion of the hitherto taboo subject of impotence. "But even what I thought were respectable journals played up the titillating aspects and ignored any attempt at scientific accuracy," he says. A *Mother Jones* story on his work, for example, ran a picture of Davidson with a caption that read, "I'd love to turn you on."

Davidson's notoriety actually began with a strictly scientific search: as a part of studies on the brain and sexual behavior, he was looking for a neurophysiological mechanism to explain the decreased libido and impotence that men occasionally experience during treatment for high blood pressure.

Many medicines lower blood pressure, Davidson explains, by binding to special sites in the central nervous system called adrenergic receptors. This inhibits release of the hormonal neurotransmitter norepinephrine, which controls, among other body functions, the contraction of smooth muscles in arterial walls. When norepinephrine release is inhibited, smooth muscles relax, arteries dilate, and blood pressure drops. Unfortunately, in some cases, so does sex drive.

With research associate Erla Smith and graduate student John Clark, Davidson injected male rats with a commonly prescribed antihypertensive drug that activates both of the two types of alpha-adrenergic receptors. The drug, says Davidson, induced "a devastating effect on sexual behavior—no motivation for mating, no evidence of sexual arousal." And the larger the dose, the more pronounced the sexual inhibition. Curious to see if the inhibition was linked to just one of the two receptor types, Davidson and his coworkers attempted to reverse the effect by administering a drug that obstructed only the alpha-1 receptors. There was no improvement in the rat's sexual performance. Then they tried yohimbine, which binds only to alpha-2 receptors, and found that it completely counteracted the sexual inhibition caused by the hypertension drugs. Even more eye-opening, a control group that hadn't received the hypertensive drugs before getting yohimbine displayed sexual activity significantly above normal.

In the August 24, 1984, issue of *Science* Davidson wrote, "These data suggest that yohimbine may be a true aphrodisiac, since it increases arousal in sexually experienced male rats, facilitates copulatory behavior in sexually naive males, and induces sexual activity in males . . . previously . . . inactive." That started bells ringing in places Davidson never anticipated.

The January 1, 1985, issue of *Star*, a national news tabloid, for example, contained an article mentioning Davidson's research under the headline "'Love potion' from tree works wonders for impotent men, report scientists." It quoted Davidson as saying, "We've been having amazing results with our tests on men," and contained effusive encomiums such as that attributed to a Palo Alto chemist: "Since I started with Dr. Davidson, I've been able to make love successfully many times to my long-suffering wife. She thinks she's won the pool." The only problem with such praise, Davidson observes, is that the Stanford team had not yet tried yohimbine on humans.

Stanford's legal department demanded a retraction, but by then Davidson was already being inundated with letters from husbands and wives all over the world begging for help, including supplicants from Italy whose letters began, "Caro Professore Aphrodisiaco."

Davidson is touched by such letters and thus doubly irritated by companies marketing mail-order yohimbine-related products. One sends its promotional material in an envelope emblazoned with "The cure for sexual impotence" in large red type. "You have to read the fine print underneath the beautiful graphics reproducing our work," says Davidson, "to learn that the 'inexperienced males' are rats, not people."

So will yohimbine help impotent men? Davidson will only say that years of research remain to be done. "But I do believe that pharmacologic treatments for impotence will be discovered," he says. "Hopefully soon."

—*Stephen Levit*

Another (Yawn)

BY ALICE KAHN

There may be a million yawn-orgasm stories in the naked city, but it was news to me. And I was determined to get to the bottom of it.

The facts are these: A friend sent me a clipping from Omni magazine alerting me to a tidbit of Amazing Science published in the august Canadian Journal of Psychiatry (Vol. 28, pp. 569-570). It seems that three obscure clinical psychiatrists in the provincial town of Saint John, New Brunswick, had inadvertently caught the attention of a Believe-It-or-Not-hungry nation, but this story was true.

The Canadians had uncovered "Unusual Side Effects of Clomipramine Associated with Yawning." That was the title of their paper describing four patients who, while taking the anti-depressant drug clomipramine (trade name: Anafranil) reported the unusual side effect of spontaneous orgasm every time they yawned.

The good doctors were alerted when one patient who had been markedly depressed for three months took the drug and — shazam! — "Complete symptom remission occurred within 10 days." OK, she got over her depression awfully fast, but then she asked how long she would be "allowed" to continue the drug.

When the suspicious clinician questioned why she wanted to continue, the scientific paper reports, "She sheepishly admitted that she hoped to take the medication on a long-term basis, not so much because of the symptom relief that she had experienced, but rather because she had noted that since taking the medication, every time she yawned she had an orgasm. She found she was able to experience orgasm by deliberate yawning."

Think of the possibilities here. Imagine, if you will, a world in which "The Best of Carson" might become a stimulant!

Another male patient, reporting similar symptoms, said that while he found the repeated climaxes "awkward and embarrassing, he elected to continue the medication because of the therapeutic benefit he obtained. The awkwardness and embarrassment were overcome by continuously wearing a condom."

A second male patient however, less devoted to cure, discontinued the medication because "every time he yawned he experienced such an intense sense of exhaustion and weakness that he had to lie down for 10 or 15 minutes after each yawn."

Your reporter got on the case.

First I determined that there had been no reports of a run on Canadian pharmacies following the journal article. Further, there haven't been any reports of a rise in the number of patients complaining of symptoms of depression.

At Ciba-Geigy, the company that markets clomipramine in Canada and Europe, I was referred to a Miss Norekio, who monitors drugs for the firm. She explained that the drug is not available in the United States because the requisite number of FDA studies have not been performed.

"But hasn't the company been interested in exploring this unusual side effect?" I inquired by phone.

"I'm not the person to ask. I have no overall view of adverse experience with the drug on a worldwide basis," Norekio said in the careful manner of one who is speaking for a Big Company.

But faster than you can say Mike Wallace, I shot back, "Do you regard this as an *adverse* experience?"

"I don't know anything about it," she insisted when pressed for a response to the Canadian psychiatrists' report. "... but I did hear people in the elevator talking about it."

"The article wasn't intended to have a big response," says Dr. I. A. Kapkin, one of three authors of the journal report. "It was meant to alert clinicians to an effect that hadn't been reported." Speaking from his home in New Brunswick, Dr. Kapkin explained the genesis of

Orgasm Story

BY ERIC LUSE

his unusual paper:

"There is considerable yawning and sleepiness reported with anti-depressants, but we had patients reporting, simultaneously, 'funny' side effects. We had to ask: 'What is funny?' "

Thanks to the doctor's perseverance, mankind now knows "what is funny."

"This is only observation, not research. It's a side effect, not a therapeutic effect," insists the appropriately cautious Dr. Kapkin, although a layman might argue that such a side effect *is* therapeutic.

"There was no suggestion to use the drug on sexual disorders," he says in response to my asking whether that possibility had been explored, "... although U.S. physicians have raised the question of using the drug for other purposes."

Dr. Lynn Meyers, who conducts research in the Stanford University Treatment Program for Impotence, notes that clomipramine did cause yawning in rats, although she was unaware of its causing orgasm. "There's been nothing on that besides the Canadian paper."

First, I inquire tactfully about how one knows a rat is yawning. "A rat just opens its mouth and yawns just like us, but they don't put their little paws up to their face."

Next I inquire how the phenomenon of orgasm is observed in rats, thinking for a moment that, in today's atmosphere of laboratory animal abuse, the lucky rat who lands in Dr. Meyers' cage is in for a treat. "It hasn't been established yet that any female animal other than monkeys are known to orgasm," she said, alluding to a fellow scientist who got a grant from the National Institutes of Health to study orgasm in free-range female monkeys.

Dr. Meyers, however, was able to cite research done at Stanford in which male monkeys were observed exhibiting "mounting behavior and erection" when given Yohimbine, a tree bark extract that is known to be an aphrodisiac in rats. "In fact, some guy in *Stamford,* Connecticut, opened up a storefront to sell Yohimbine, calling it The Stamford Research Center. He put out a brochure showing smiling African natives with erections and quoted *Stanford* research on Yohimbine. It got real sticky."

Dr. John Buffum, a research pharmacologist at the University of California-San Francisco and the author of a major review paper, "Pharmosexology: The Effect of Drugs on Sexual Function," said the Canadian Journal report "stands out. There are no other reports of yawns and orgasms. I've never run across a reaction like that. There are other articles showing that it causes dysfunction," and in fact the same Canadian Journal of Psychiatry had published one such report a year before Kaplan et al announced their findings to a bemused if not breathless world.

The question of how the anti-depressant may lead to yawning and orgasm is one that has intrigued and eluded the scientists.

San Francisco psychiatrist Harvey Caplan, who specializes in sexual disorders, said, "There is a syndrome of when some people have orgasm they have fits of sneezing. And many people have a stuffy nose after orgasm."

"How that relates to yawning, I don't know. I guess all we can say is the head is connected to the genitals somehow," he said laughing.

First yawning, now sneezing — there may be another story here.

"The only other slightly comparable report," notes Dr. Glenn Peterson, an Oakland psychiatrist, "... is of a type of epilepsy driven by photic stimulation — flashing lights, phone poles going by — that triggers an orgasmic response."

I leave it for other investigators to pursue this phenomenon.

Dr. Kapkin, who still doesn't understand why a few of his patients on clomipramine had this idiosyncratic response, thought it might be related somehow to endorphins in the brain. Endorphins are naturally produced opiate-like substances.

Says Kapkin, "The only similar phenomenon we know of is that of the American Society of Magazine Editors for best monthly under

therapeutic.

"There was no suggestion to use the drug on sexual disorders," he says in response to my asking whether that possibility had been explored. "... although U.S. physicians have raised the question of using the drug for other purposes."

Dr. Lynn Meyers, who conducts research in the Stanford University Treatment Program for Impotence, notes that clomipramine did cause yawning in rats, although she was unaware of its causing orgasm. "There's been nothing on that besides the Canadian paper."

First, I inquire tactfully about how one knows a rat is yawning. "A rat just opens its mouth and yawns just like us, but they don't put their little paws up to their face."

Next I inquire how the phenomenon of orgasm is observed in rats, thinking for a moment that, in today's atmosphere of laboratory animal

[redacted] why did he start the magazine?

"The only other slightly comparable report," notes Dr. Glenn Peterson, an Oakland psychiatrist, "... is of a type of epilepsy driven by photic stimulation — flashing lights, phone poles going by — that triggers an orgasmic response."

[redacted] phenomenon.

[redacted] a few of the patients [redacted] idiosyncratic response, though it might be related somehow to endorphins in the brain. Endorphins are naturally produced opiate-like substances.

Says Kapkin, "The only similar phenomenon we know of is that, with opium withdrawal, people sometimes experience yawning and spontaneous orgasm." He referred to a letter published in the Canadian Journal of Psychiatry that followed his paper. Four New York doctors attempted to explain the yawn-orgasm effect in terms of a complex biochemical reaction associated with increased brain levels of the neurotransmitter serotonin. Clomipramine is known to act on serotonin levels.

Whatever the explanation, all agree that the yawn-orgasm patients' reports of complete remission of depression in 10 to 14 days are a bit unusual also. Says Dr. Peterson, "I don't now how you tie in an unusual sexual response with recovery — you don't have to produce multiple orgasms to get a complete anti-depressant response. That would be an awkward kind of link."

Again it might be left to the layman to explain to the scientist why, under the circumstances, his patients were no longer depressed.

Interestingly, the company that might profit from such a link being made is uncomfortable with the research. Several people with whom I talked at Ceiba-Geigy, who did not want to speak officially, expressed fear of sensational publicity over what is, after all, an unusual side effect. It occurred in a handful of people out of hundreds who have taken the drug.

It should also be noted that broader studies show that 26 percent of the males and 14 percent of the females using clomipramine reported adverse — truly adverse — effects on sexual performance.

Still, it is human nature to home in on the bizarre, the unusual, the funny sex story. Virtually everyone I know who saw the yawn-orgasm report was amused and wanted to know more. That's what prompted this investigation on everything you ever wanted to know about yawns and orgasm.

The only person who seemed indifferent was one friend who said of his wife of 21 years, "This is nothing new to us old, married people. My wife yawns every time she has an orgasm."

Berkeley writer Alice Kahn is the author of "Multiple Sarcasm," published by Ten Speed Press.

Love

Continued from Page E-1

Suppose that a handsome lad and a beautiful girl — let's call them Jack and Jill — happen to meet on, say, Valentine's Day. It seems that Jack has a mostly unconscious image in his mind of the perfect woman: her face, her form, the way she talks and the way she walks. And so he meets the lovely Jill.

"Suddenly he discovers that his heart is racing," Liebowitz said, "his breath is coming faster and he has a feeling of excitement, happiness and anticipation."

In fact, he said, Jack's reactions to Jill closely resemble the way Jack would feel if he had taken a stimulant like amphetamine or cocaine.

Amphetamine is believed to affect the human nervous system indirectly by inducing the brain to release vast amounts of the neurotransmitters norepinephrine and dopamine. It does so in a way that is little understood, perhaps involving a naturally occurring amphetaminelike substance in the human brain called phenylethylamine.

Results from a variety of recent research projects have led scientists to hypothesize that there are amphetaminelike fluctuations in the brain in response to emotional phenomena as disparate as rejection and falling in love.

Liebowitz believes that neurochemical pathways in humans, somewhat analogous to electrical circuits wired into machines, facilitate the response we call romantic attraction. "Essentially what happens is that someone walks along who fits that notion we have of attractiveness," Liebowitz said, "and, well, ka-pow."

The action of the chemicals norepinephrine and dopamine is believed to affect the threshold, or activation level, of the brain's pleasure center. Studies with animals have located this region in the limbic system, the brain network responsible for emotional experience.

It is, Liebowitz believes, the stimulation of the brain's pleasure center that accounts for Jack's decidedly enjoyable sensations, and the more he sees of Jill the more pleasure he feels. Even better, he fits the pattern she finds attractive — and so Jill's response parallels Jack's.

"To the extent they reciprocate, then they keep this whole reaction going," Liebowitz said. And what is this reaction? However scientists might describe it, Jack and Jill would certainly call it falling in love. "Love and romance seem to be one of the most powerful activators of our pleasure centers," Liebowitz said.

Sometimes lovers may achieve a special romantic state. "It is a transcendent feeling," Liebowitz said, "a feeling of being beyond time, space and your own body."

Such states closely resemble descriptions of psychedelic experiences. The action of psychedelic substances such as LSD, mescaline and psilocybin involves a number of brain chemical systems, including that associated with serotonin, another neurotransmitter.

"I think that these peak love experiences involve such intense stimulation and joy," Liebowitz said, "that some additional neurochemical reaction is triggered, which may be similar to whatever the psychedlic drugs do to our brains."

"Of course, the peak cannot last," Liebowitz said. "The great romances of literature are the stories of people who have been thwarted from being together for any length of time."

There is, nevertheless, a powerful bond between romantic lovers who have become spouses. "It is the difference between attraction and attachment," he said. "They are both different aspects of love. Attachment is associated with warm feelings that may be calming or comforting."

Liebowitz said that the joys of attachment may be associated with the lessening of anxiety, which involves subtle alterations in the chemistry of yet another brain network. Researchers are trying to determine if an area in the brain stem known as the locus coeruleus acts as an alarm center in humans, regulating feelings of anxiety, panic and depression.

In addition, Liebowitz believes, the pleasurable feelings of attachment are associated not just with the brain's pleasure center but also with the brain's production of its own narcotics. These soothing substances, called endorphins, may be secreted in situations of social comfort.

Both kinds of love, attraction and attachment, could have been evolutionarily desirable, Liebowitz said. "A prerequisite for our species to survive," he went on, "was that, first, adults would be attracted to one another to mate, and, second, that the offspring would be protected so they can survive their long period of helplessness. Attachment not only tied mothers and infants together for long periods of time but also kept the fathers involved."

This second kind of love can be just as gratifying as the thrill of early romance, he said. Unfortunately, many of us confuse the two kinds of love, which may have very different biochemical bases.

"It's difficult to keep an ongoing relationship romantic, to achieve the same peaks of love," Liebowitz said. In the natural process of acclimation, lovers achieve a measure of toleration or adaptation to each other and the thrill is gone.

"Yet in our culture we demand that our relationships continue to be romantic," he said. "I think it's because the media constantly portray only one sort of love as desirable — attraction, rather than attachment."

The book Liebowitz, 37, has written is called "The Chemistry of Love" (Little, Brown, $15.95). It is based in part on his research at the New York State Psychiatric Institute at Columbia Presbyterian Medical Center in association with Dr. Donald F. Klein, the institute's director.

Liebowitz does not believe investigating the chemistry of love diminishes the importance of social and psychological factors. "We still don't know how a change in brain chemistry becomes a feeling," he said.

"The importance of love has nothing to do with brain chemistry," he said. "It has to do with the depth and variety of the pleasures experienced. Love is an opportunity for learning, and a way to enhance our lives."

Increased Libido in Women Receiving Trazodone

Nanette Gartrell, M.D.

The author presents the cases of three depressed women whose libido increased to above premorbid levels during trazodone treatment. Two patients resisted discontinuing the drug because of this pleasurable side effect.

(Am J Psychiatry 143:781–782, 1986)

Although clinicians have been alerted to the possible association between trazodone and priapism (1, 2), a review of the literature failed to reveal any information about trazodone's effects on female sexual functioning. I have used trazodone to treat major depression and dysthymic disorder in a variety of female patients in the past 3 years. In this report I describe three cases of depressed women who experienced an increase in libido to above premorbid levels with therapeutic doses of trazodone.

CASE REPORTS

Case 1. Ms. A, a 26-year-old graduate student, had a 12-year history of recurrent major depression. She had no history of alcohol or drug abuse. There was no family history of affective disorder. She had never received a medication for her depression, nor had she been psychiatrically hospitalized. She had had only one sexual relationship, which had terminated 2 years before referral. She had not masturbated for over a year, and she had never been orgasmic.

Ms. A was referred for treatment after she failed to complete a series of courses because of her inability to concentrate on her work. At the time of her referral, she had been experiencing anhedonia, hypersomnia, anergy, excessive guilt, and suicidal ideation for 6 months. Her treatment began with a regimen of trazodone in gradually increasing doses up to 150 mg/day. Her symptoms began to remit when she reached 100 mg/day. At 150 mg/day she experienced increased energy, less preoccupation with guilt, and fewer suicidal fantasies. She also reported that her sex drive was greater than it had ever been. She began masturbating daily. Even though she continued to be anorgasmic, she initiated two new sexual relationships.

At the time of this report, Ms. A had been taking trazodone, 150 mg/day, for 3 months. She had no residual symptoms of major depression. She was enjoying the libidinal stimulation she attributed to the trazodone and expressed a concern that eventual discontinuation of the trazodone would inhibit her sexual pleasure.

Case 2. Ms. B, a 44-year-old psychologist with good premorbid functioning, had a 2½-year history of dysthymic disorder that had begun after a mastectomy and relationship loss. She suffered from chronic fatigue, social isolation, and poor self-esteem. Whereas she had previously had positive and satisfying sexual relationships, her sex drive had diminished to the point that she had given up masturbating.

After a year of psychotherapy and no remission of symptoms, Ms. B agreed to a trial of trazodone in gradually increasing doses up to 150 mg/day. The week after she had begun taking 150 mg/day, she reported that she thought trazodone might be an aphrodisiac. Although she was orgasmic, as she had been before the onset of her dysthymic disorder, she began to feel as though she was constantly sexually driven. She began masturbating again, and she also reestablished sexual relationships with three former sexual partners (she had previously been sexually monogamous). Concurrently, her level of energy improved and she regained her self-confidence.

Ms. B's trazodone was tapered off 6 months later. Although she did not experience any recurrent symptoms of depression, she did lament the diminution of her sex drive to its premastectomy levels within 2 weeks after discontinuing the trazodone. She continued to have no depressive symptoms.

Case 3. Ms. C, a 34-year-old business executive, had a 3-year history of dysthymic disorder. She was tearful and self-deprecatory most of the time. She was also socially withdrawn and pessimistic about the future. She did not abuse drugs or alcohol. She had no family history of affective disorder, and she had had no previous psychiatric treatment. She had been neither sexually active nor masturbatory since the termination of a relationship 3 years previously.

When Ms. C showed no improvement after 10 months of psychotherapy, she was begun on a regimen of trazodone in gradually increasing doses. Several weeks after she reached the dose of 150 mg/day, she reported that she had begun to experience an increased sex drive. She had begun masturbating again, and she had also been willing to accept invitations to social activities, which she had previously shunned. She soon became involved in a new relationship. She reported that her sex drive was greater than it had ever been and that she was orgasmic more frequently than ever before.

Ms. C's trazodone was tapered off after 7 months. Although she reported a diminution in her libido within a week after the trazodone was discontinued, she remained professionally active and nondepressed. However, when her rela-

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tionship terminated, she began to experience a recurrence of her depressive symptoms. The trazodone was reinitiated, and again Ms. C reported a substantial increase in libido 11 days after she began taking 150 mg/day. Her remaining symptoms of depression remitted over the following month. She had continued to be euthymic while taking trazodone, 150 mg/day, at the time of this report.

DISCUSSION

To my knowledge this is the first published report of increased sexual drive above premorbid levels in women receiving therapeutic doses of trazodone. At the time of this report the manufacturer of trazodone had obtained information about only one case in which a woman described increased libido associated with trazodone. Of the 13 women I have treated with trazodone, six—including the three cited in this report—experienced a substantial increase in libido coinciding with a remission of depressive or dysthymic symptoms, five experienced no therapeutic or libidinal effect, and two experienced a remission of depression without libidinal effects. Although I routinely inquire about changes in sexual functioning with antidepressant treatment, I have never had a patient who was taking an antidepressant other than trazodone acknowledge an increase in libido to above premorbid levels. The fact that 46% of my very small sample of female patients receiving trazodone reported libidinal stimulation suggests that this side effect may occur more frequently than clinical trials have indicated (3–5).

It is important to point out that the increased libido experienced by these patients was described as highly pleasurable. None of the patients had received any information about possible libidinal side effects of trazodone before initiating treatment. In fact, when these patients realized that the increased sex drive might be associated with trazodone, they were reluctant to discontinue the medication.

Trazodone has been shown in animal studies (3) to decrease prolactin levels, to inhibit reuptake of serotonin, to produce β-receptor subsensitivity, and to decrease $5\text{-}HT_2$ binding. Since our understanding of the neurophysiology of the female sexual response is still very primitive, further studies will be necessary to determine whether any of trazodone's known neurochemical actions are related to the increased libido that some women have reported.

I hope that controlled clinical trials examining sexual functioning in both female and male patients will provide more information about the effects of trazodone on libido. I would also like to encourage my colleagues to inquire about increased libido in patients who are receiving trazodone. We so often experience the problem of patient noncompliance because of adverse antidepressant side effects that we do not anticipate encountering drugs whose side effects are so pleasurable that patients are reluctant to stop taking them.

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Dopaminergic Drugs and Sexual Behavior

The role of dopamine-receptor antagonists in the development of impaired sexual function has been amply documented (see *Psychiatric Capsule & Comment*, February 1983). Reduced sexual drive and impotence are frequent side effects of such drugs, probably at least in part as a result of the increased prolactin blood levels caused by neutralization of the normal dopamine-induced inhibition of prolactin secretion (see *Psychiatric Capsule & Comment*, January, 1983). On the other hand, ever since the introduciton of levodopa for the treatment of parkinsonism, there have been reports indicating that some patients experience a striking increase in libido, although some authors have at least suggested that this may have been "a return to normal" rather than a manifestation of "hypersexuality."

or impaired follicular maturation (recovery ore lik halet 1980). About 50% of women tre with combin chemotherapy will become orrheic. Prepubertal pubertal gonadal on may be damaged by cl herapy, alth there is a possibility that the prep al t y be less susceptible to damage than the pub is (Shalet 1980).

When attempti ne gonadal dysfunction due to chem apy, it is ant to know the pretreatm nction. On the pretreatment semen a s, it has been shown that le cancer p already have low sperm counts (Tha vett uer 1981).

Carbon Disulfide

Carbon disulfide is an industrial solvent that has been associated with impotence and elevated FSH and LH levels, as a result of long-term exposure to high levels (Wāgar et al. 1981). In a study of 15 exposed men and 16 age-matched controls, 10 of the 15 had reported some degree of impotence at some time. Eight men still complained of occasional or total impotence. None of the controls reported impotence. Most of the men felt that the impotence was worse in the past when the allowable exposure levels were higher (above 10 ppm). The duration of exposure was between 10 and 36 years. Serum testosterone was normal. This, along with the elevated FSH and LH levels, and normal thyroid-stimulating hormone (TSH) and serum prolactin (PRL) responses to TSH was taken as a sign of "latent" primary gonadal insufficiency. The men were not withdrawn from exposure to carbon disulfide and no sex therapy was attempted, so it is not known to what extent the impotence was reversible or even real (Wāgar et al. 1981).

DRUG ENHANCEMENT OF SEXUALITY

True aphrodisiacs have been traditionally thought of as substances that are capable of stimulating sexual interest in someone with no other sexual stimulus present. When testing for aphrodisiacs the animal model breaks down. Drugs shown to stimulate animal sexual behavior have not been shown to do the same in humans. There are, however, many substances that tend to enhance certain aspects of sexuality in humans when the sexual inclination already exists. Some of these have already been mentioned. This section will cover the remainder of these and will also review studies on drugs that have been tested for aphrodisiac properties.

Volatile Nitrites

These are vasodilators, some of which have been used in treatment of angina pectoris (Sigell et al. 1978). These compounds are currently used for the enhancement of sexual pleasure. They are reputed to prolong orgasm, or the perception of orgasm, following inhalation prior to orgasm (Sigell et al. 1978). They are also thought to relax the anal sphincter to facilitate anal intercourse, especially in the male homosexual community (Labataille 1975). To date, there are no substantiating studies that prove or disprove these effects. The mode of action for the prolongation of orgasm is unknown. One author (Louria 1970) thought it might be due to cerebral ischemia, although that would be doubtful, considering the mode of action and circumstances of use (inhalation while lying down). The vasodilation with reflex sympathetic compensation could have an effect on the perception of orgasm (Kramer 1977). When volatile nitrites are inhaled too soon, prior to orgasm, the result can be immediate detumescence rather than an enhanced orgasm. This effect has been used clinically during cystoscopy and following adult circumcision to prevent unwanted erections (Welti & Brodsky 1980).

Bromocriptine Mesylate (Parlodel®)

Bromocriptine mesylate is an ergot derivative and dopamine agonist that is used to inhibit the secretion of prolactin by the pituitary in hyperprolactinemic states (March 1979). Because of the association of dopaminergic stimulation with increased sexual activity in animals, it was felt that a dopamine agonist might be useful in the treatment of impotence (Glassman, Rife & Wilson 1980; March 1979; Soyka, Joffe & Smith 1979; Carter et al. 1978; Ambrosi et al. 1977; Cooper 1977; Innes & Nickerson 1975b; Thorner et al. 1974). Hyperprolactinemia causes amenorrhea and galactorrhea in women, and impotence, loss of libido and oligospermia in men (Glassman, Rife & Wilson 1980; Carter et al. 1978). It is not clear exactly how hyperprolactinemia decreases sexual function. Magrini et al. (1976) felt that increased levels of prolactin decreased the conversion of testosterone to its active form, dihydrotestosterone, by inhibiting the necessary enzyme, 5 alpha-reductase. Two studies done in hyperprolactinemia patients with pituitary tumors, showed a restoration of sexual function and normalization of prolactin levels in some cases, with doses of five to 10 mg/day (Carter et al. 1978; Thorner et al. 1974).

Renal failure patients on chronic hemodialysis are frequently hyperprolactinemic and have decreased libido and erectile dysfunction (Bommer et al. 1979). One study showed improved sexual function in six of seven chronic hemodialysis patients with bromocriptine (5

mg/day). Two other studies done in impotent patients who had no endocrine disturbances, showed no improvement with bromocriptine (Ambrosi et al. 1977; Cooper 1977). The doses used were 5.0-7.5 mg/day. Bromocriptine appears to be useful in about 80% of patients with hypoganadotrophic hypogonadism and hyperprolactinemia (March 1979). Bromocriptine's therapeutic effects are due to its direct effects on pituitary lactotrophs to inhibit prolaction secretion, activitation of the dopamine receptors of the lactotrophs and action on hypothalamic centers (March 1979).

Levodopa (Larodopa®)

Levodopa (L-dopa) is a dopamine precursor used in the treatment of Parkinsonism (Franz 1975). L-dopa has been reported to cause hypersexual behavior in eight of 908 (0.9%) Parkinsonian patients being treated with it (Goodwin 1971). The author felt that the increased sexual behavior was probably part of a more general hypomanic syndrome. Hypersexuality was almost always associated with other symptoms suggestive of hypomania.

Other smaller studies drew more enthusiastic conclusions (Brown et al. 1978; Hyyppä, Falck & Rinne 1975; Benkert, Crombach & Kockott 1972). One showed an increase in spontaneous erections in six of eight non-Parkinsonian patients, but in no case was the erection sufficient for intercourse (Benkert, Crombach & Kockott 1972). Another study purported to show that approximately 50% of seven Parkinsonian patients showed increased sexual interest or activity unrelated to improved locomotor function (Brown et al. 1978). In one study, L-dopa was administered to 10 schizophrenic patients with a resultant activation of psychotic symptoms in all 10 (Angrist & Gershon 1976). Much of the acting out took a sexual form. In the same study, three of six nonschizophrenic psychiatric patients on L-dopa developed increased sexual effects. In these studies, there seemed to be a small number of patients for whom L-dopa had an aphrodisiac effect. The authors noted that the extent of the effects seemed to correlate with the amount of hypersexual behavior occurring before the drug. In their words: "Thus, we suspect that amphetamine and L-dopa might prove to have aphrodisiac effects in those who 'need' them least and not prove helpful to those who could most benefit from such effects." Another study also noted that the reports of increased sexuality seemed to occur when the Parkinsonian symptoms could still be seen (Hyyppä, Falck & Rinne 1975). When the Parkinsonian symptoms had disappeared because of the L-dopa treatment, the reports of hypersexuality tended to decrease.

There is one report of two patients developing failure of ejaculation with L-dopa (Hällström & Peterson 1970). Erection and orgasm occurred normally in conjunction with either failure of emission or retrograde ejaculation. It was not clear which occurred. The doses used were 2.5-3.0 g/day.

The mode of action for any increased libido occurring with L-dopa would probably be a result of the same mechanism reported in animals. Why this should occur in only a relatively few humans, but in most animals, has not yet been elucidated. Why L-dopa caused two isolated cases of failure of ejaculation is not clear either.

Parachlorophenylalanine (PCPA)

PCPA is an inhibitor of serotonin synthesis that has been used in the treatment of migraine headaches (Sicuteri, Del Bene & Anselmi 1975). There was an initial uncontrolled report of PCPA being associated with increased levels of sexual excitation in migraine patients (Sicuteri 1974). In one woman, "the sexual excitation was so intense that the treatment with PCPA had to be interrupted." In a later study, on male migraine patients on PCPA, oral PCPA and I.M. placebo was compared with I.M. placebo plus oral placebo or oral PCPA plus I.M. testosterone (Sicuteri, Del Bene & Anselmi 1975). PCPA and testosterone resulted in a significant increase in the total number of daily erections. PCPA alone was no better than placebo. The earlier study (Sicuteri 1974) showed that testosterone alone was also no better than placebo. Apparently, PCPA's sexual stimulation has been reported only in migraine patients, but not in normals (Sicuteri, Del Bene & Anselmi 1975). It has also been noted that there is a decrease in libido in migraine sufferers (Sicuteri, Del Bene & Anselmi 1975). Because migraines have been associated with increased serotonin levels, and PCPA decreases serotonin levels, it would be reasonable to assume that PCPA might cause increases in sexuality in migraine patients. Sicuteri, Del Bene and Anselmi (1975) felt that "the lowering of serotonin brain concentration seems to sensitize central structures involved in the sexual stimulation, therapy facilitating a trigger action of testosterone." The dose of PCPA used was 15 mg/kg per day.

Levotryptophan (Trofan®)

Levotryptophan (L-tryptophan), a serotonin precursor, has been used experimentally in the treatment of multiple sclerosis, depression and schizophrenia (Broadhurst & Rao 1977). There is one report of L-tryptophan producing hypersexuality in four male schizophrenics

and one manic depressive (Egan & Hammad 1976). The mechanism of action of the hypersexuality was not known. The schizophrenics were also on phenothiazines. The hypothesis that L-tryptophan loading may increase levels of serotonin, resulting in decreased libido has been tested (Hyyppä et al. 1975). Significant changes in sexual motivation did not occur as a result of the L-tryptophan loading in depressives, multiple sclerosis patients and normals. In another uncontrolled study on 56 headache sufferers, the author (Sicuteri 1974) felt that he could "express the impression of a reduction of sensuality." The sexual side effects of L-tryptophan do not sound very significant, with the possible exception of their occurrence in schizophrenics. The doses of L-tryptophan used were 1.5 g/day.

Yohimbine

Yohimbine is an alkaloid obtained from various plant sources, notably *Corynanthe yohimbe*. It has been used in the therapy of impotence and as an aphrodisiac (Gawin 1978). Yohimbine was incorporated into products with methyltestosterone and nux vomica as a treatment for the "male climateric" (Sobotka 1969; Miller 1968; Bruhl & Leslie 1963). As noted earlier, those products were removed from the market. Yohimbine is classified as an α_2-adrenergic-blocking agent and has been noted to be a model anxiety-producing agent (Hoffman & Lefkowitz 1980; Ingram 1962). At a dose of 0.1 mg/kg I.V., yohimbine produced all the psychic and autonomic effects of acute anxiety (Ingram 1962). The dose used for aphrodisiac properties was 5.0 mg orally (Aviado 1972).

Zinc

Zinc is an essential trace element. Several studies have noted that uremic patients, both nondialyzed and those on hemodialysis, had low plasma zinc levels (Antoniou et al. 1977). It is well known that 20%-80% of uremic men and women have a decrease in sexual function (Mahajan et al. 1980; Antoniou et al. 1977; Holdsworth, Atkins & de Krester 1977; Levy 1977; Abram et al. 1975). One study revealed "strikingly improved potency in all patients" when zinc chloride was administered at a concentration of 400 mcg/l in the dialysate fluid of four uremic patients undergoing hemodialysis (Antoniou et al. 1977). Placebo did not improve sexual function in any patient. The cause of the low blood zinc levels in uremics is unknown. Two of the four patients in the study who had had low pretreatment plasma testosterone levels had their levels raised to normal. The study indicates that zinc deficiency is a major cause of abnormalities of testosterone synthesis or metabolism in uremia. Oral zinc sulfate, providing 100 mg/day elemental zinc, increased plasma zinc levels slightly in three of the four uremics with minimal improvement in sexual function (Antoniou et al. 1977). The authors speculated that intestinal absorption may be faulty in uremics.

In another double-blind randomized study of 20 male uremic hemodialysis patients taking oral zinc acetate, the provision of 25 mg elemental zinc (presumably the daily dose) was compared with placebo in the relief of sexual dysfunction (Mahajan et al. 1980). In the 10 control dialysis patients there was no improvement in sexual function as assessed by questionnaire. In the 10 zinc treatment patients, erectile ability improved in seven of the eight impotent patients. Libido increased in all four of the patients who had complained of decreased libido, and frequency of intercourse increased in seven of the nine patients who complained of decreased frequency. Plasma zinc, serum testosterone and sperm counts increased significantly in the zinc treatment group but not in the placebo group. It is unclear why this study obtained better results from lower doses of oral zinc than the study by Antoniou et al. (1977). Results of these studies suggest that zinc deficiency may be a major cause of abnormalities in testosterone synthesis or metabolism in uremics.

Older patients have been shown frequently to have low preoperative serum zinc levels Hallböök & Hedelin 1977). It has also been noted that Atlantic oysters have a particularly high zinc content (about 50-100 times that found in most foods) (Murphy, Willis & Watt 1975). Combining these two facts leads to some interesting speculation on the almost legendary aphrodisiac properties of oysters in tired elderly men.

Pheromones

Pheromones are hormonal substances secreted by animals, which attract members of the opposite sex through their olfactory sense (Keverne 1977). Work on human pheromones is in its infancy, but it is known that these substances, secreted by females of lower species, have very powerful sexual-attracting capabilities on the males of the same species. One study isolated some short-chain fatty acids from the vaginal secretion of human females, which were thought to be crucial pheromonal components (Sokolov, Harris & Hecker 1976). α Androstenol, a pheromone isolated from human male sweat, has been tested by the perfume industry. It was found to be so attractive to human females that it has been incorporated into new aftershaves and men's colognes (Durden-Smith 1980). Pheromones may prove to be the only true aphrodisiacs.

Clomiphene Citrate (Clomid®)

Clomiphene citrate is an antiestrogen frequently used in the treatment of ovulatory failure in women desiring pregnancy (Murad & Gilman 1975b). There is a single case of the drug being used in a sexually dysfunctional male alcoholic in an attempt to reverse the feminization resulting from his cirrhosis and testicular atrophy. Its use resulted in increased testicular size, resolution of impotence and increased libido (Bjork, Varma & Borkowf 1977). The dose used was increased from 50 to 200 mg/day over a four-month period, although it was felt that 50 mg/day would have provided maximal response. The patient's improvement lasted eight months after treatment was stopped, at which time his sexual function reverted to his pretreatment status.

Luteinizing Hormone Releasing Hormone (HRF®)

Luteinizing hormone releasing hormone (LHRH) is a hypothalamic decapeptide that regulates LH release from the pituitary and potentiates sexual behavior in animals (Moss 1978). LHRH has been shown to increase mating behavior in female rats and facilitate intromission and ejaculation in male rats (Moss 1978). The response in female rats is more pronounced. These observations led to its use in humans to see if it had a similar effect on human sexual response. LHRH has been injected or used as a nasal spray in sexually impotent men with ambiguous results. Moss (1978) described a study in which LHRH (500 mcg/injection) administration to eight impotent males resulted in immediate increased sexual activity.

In another double-blind crossover study done with 20 impotent men, one mg/day of LHRH was given over a four-week period by nasal spray (Benkert 1980). The LHRH group showed increased sexual activity four to six weeks after discontinuing the drug. In a third double-bline crossover study done with 10 impotent men, no obvious clinical improvement occurred following the administration of 500 mcg/injection of LHRH every eight hours over four weeks (Davies et al. 1976). Statistical analysis showed some improvement in libido scores and spontaneous erections.

Results in normal (not impotent) males have been disappointing. Moss (1978) described two studies conducted with normal males. One showed increased sexual interest following injection of an unspecified amount of LHRH in an unspecified number of males. The other study showed no effect in six males after a course of 700 mcg/week I.V. (three subjects) and 250-300 mcg/week I.V. (three subjects). A double-blind crossover study done on six normal adult males, showed "consistently greater" changes following LHRH (500 mcg I.M.), as measured by rapid onset of erection, maximum degree of erection obtained and overall levels of tumescence when compared to a saline placebo (Evans & Distiller 1979). These changes were not statistically significant however. LHRH studies done in hypogonadal men have been more promising. Moss (1978) described two studies in which hypogonadal men were given courses of LHRH therapy. One of the studies showed "increased potency" in 12 men, following administration of 500 mcg injections of LHRH every eight hours for several weeks. In the other study, four hypogonadal oligospermic men showed "increased libido and sexual potency" following one month of treatment with 500 mcg of LHRH (dosage interval not specified). A study done in 21 normogonadotrophic oligoasthenospermic males showed that when 500 mcg/day of LHRH was given for 60- and 30-day periods there were spontaneous reports of increased libido and potency by 15 of the men, 20 to 30 days after the start of administration (Aparicio et al. 1976). A double-blind crossover study of 10 impotent diabetic males, given 500 mcg/injection of LHRH every eight hours, showed no significant improvement over placebo (Levitt et al. 1980). Both placebo and LHRH treatment resulted in significant improvement from baseline in the parameters measured: sexual function and libido, erectile potency and general well-being. The study specifically excluded patients with obvious vascular or neurological disease.

The studies done so far are too small and the results not conclusive enough to say whether or not LHRH would be useful in the treatment of male sexual dysfunction. To date, no studies have been done in human females, but because the LHRH-induced sexual response is more pronounced in female rats, human females might also prove to have a greater response.

Naloxone (Narcan®)

Naloxone is a narcotic antagonist used clinically to reverse the effects of opiates and endorphins by specifically blocking opiate receptors (Jaffe & Martin 1975). It has been determined that certain exogenously administered endorphins block sexual behavior in sexually experienced male rats, and that narcotic antagonists such as naloxone and naltrexone prevent this block (Gessa & Paglietti 1979). Naloxone also induces copulatory behavior in sexually inactive rats by blocking the endogenous endorphins, which would otherwise block sexual behavior (Gessa & Paglietti 1979). In sexually active male rats naloxone does not stimulate further sexual behavior, suggesting that "during sexual arousal there is not tonic stimulation of opioid receptors involved in the control of sexual behavior" (Gessa &

Paglietti 1979). The authors speculated that endorphins may play a role in rat sexual inadequacy.

There are very little data concerning the effects of endorphins and narcotic antagonists in humans. In one study, conducted on one 35-year-old male subject, three mg or 10 mg of naloxone was administered I.V. and the subject self-evaluated his own response to masturbation (Goldstein & Hansteen 1977). There were no differences in sexual arousal, penile erection, ejaculation or orgasm when compared with placebo. Goldstein & Hansteen (1977) concluded that "endorphins are not involved in these phenomena."

Perhaps further studies need to be conducted using sexually inactive human males before endorphins are ruled out as mediators of sexual behavior. It did seem to make a difference in the rats.

EVALUATION OF THE LITERATURE

When evaluating the current literature one would like to see well-designed studies with solid conclusions on which clinical judgments can be made regarding drug selection. There are very few such studies in the literature of drug-induced sexual dysfunction. Most data about the sexual side effects of drugs are generated as a result of studies addressing other questions, and some data come by way of isolated case reports. This is further compounded by review articles that do not critically analyze the data they cite. For a study to provide useful data, certain criteria should be met:

1. Frequently, studies do not mention how many males and females completed the study. This makes incidence data rather difficult to interpret, especially if the authors are talking about impotence or failure of ejaculation.

2. There should be some sort of control group, so that one can tell how the study population does when not on the drug. Certain populations have a higher incidence of sexual dysfunction, even when not on drugs (hypertensives, for example) (Bulpitt, Dollery & Carne 1976).

3. The age range of the study population should be stipulated. A decrease in sexual activity is sometimes associated with increasing age. Men sometimes have difficulty in maintaining erections as they approach old age (Levine 1976; Karacan et al. 1975; Reckless & Geiger 1975; Bulpitt, Dollery & Carne 1974).

4. It should be specified if subjects are on any other drugs. It is rather difficult to draw conclusions if the specific drug that is causing the problem is not known.

5. Most studies do not mention how the information was obtained. There can be a big difference in the results depending on whether a patient is interviewed, given a questionnaire or has simply volunteered the information (Costa, Ambrosioni & Magnani 1979; Alexander & Evans 1975; Bulpitt, Dollery & Carne 1974; Prichard et al. 1968). An example of this is the reported incidence of sexual side effects of antihypertensives. When data were collected as a result of spontaneous reporting by the patients, the incidence of impotence was 10% (Prichard et al. 1968), but when the patients were questioned regarding side effects, the incidence was 26%. In another study, also comparing methods of data collection, direct questioning of the patients resulted in a 28% incidence of impotence (close to the 26% above) (Bulpitt, Dollery & Carne 1974), but when the patients were given a questionnaire to fill out in the privacy of their own home the incidence was 47%. A third study, comparing a questionnaire to direct questioning by a physician, resulted in a 37% incidence of decreased libido with the questionnaire and none with direct questioning (Costa, Ambrosioni & Magnani 1979).

6. It is important to know at what dose the dysfunction occurred, or whether or not that dose was adequate to treat the problem.

7. It is useful to know if there is any prior history of sexual problems before starting the drug. Some patients have been known to use a drug as an excuse for not having sex.

8. Some studies use the term "impotence" without defining it. Impotence has been used for everything from decreased libido to failure of ejaculation. It is most commonly used to indicate erectile failure.

9. Not all studies can use a double-blind design, but it helps to eliminate any placebo effect or bias if neither the patient nor the researcher knows what is being ingested.

10. Randomization of the patients helps prevent any bias in patient selection. Again, not all studies can be set up in this way, but the data would be more reliable if they were.

11. Crossover design allows comparison of the patient response with and without the drug. Differences in patient response tend to show up with this design.

12. It is useful to know how long the patient was on the drug before the sexual dysfunction began, and how long the dysfunction lasted. Did the patient come to tolerate the effects of the drugs? How long did the dysfunction last before the drug was discontinued?

13. It is important to know if the patient had any other disease state or postsurgical condition which might make him/her prone to sexual dysfunction. Most studies do not indicate this.

14. Was there a method used to verify compliance

"Hypersexuality" and Behavioral Changes in Cats Caused by Administration of p-Chlorophenylalanine

Abstract. *The behavior of 26 male cats was systematically observed before, during, and after daily administration of the tryptophan hydroxylase inhibitor, p-chlorophenylalanine. These observations established that "hypersexuality," increased aggression, and perceptual disorientation are sequelae of the chronic administration of the drug in cats.*

During an electroencephalographic study of sleep patterns in cats undergoing treatment with the tryptophan hydroxylase inhibitor, *p*-chlorophenylalanine (PCPA), rather striking changes in sexual behavior were noted in one of the animals (*1*). This observation suggested that the induction of major behavioral disturbances by chronic administration of PCPA was a viable possibility, despite the lack of behavioral findings other than the induction of insomnia attributable to the chronic administration of PCPA (*2*, *3*). Accordingly, we undertook systematic and comprehensive observations of a variety of feline behavior patterns, and, in addition, we made polygraphic recordings. We summarize here the most dramatic behavioral findings of the overall study, portions of which have been presented elsewhere (*4*).

Twenty-six adult, male cats, each weighing 2 to 5 kg, were the subjects. Thirteen were observed according to a standard protocol on at least four occasions before the onset of treatment (base line) and throughout the treatment period (group A). The remaining 13 animals (group B) were studied according to the same systematic procedure during the course of other PCPA experiments, but less regularly.

The data were derived mainly from standard behavioral test sessions, each 1 hour long, during which the cats were continuously observed in a specially constructed, isolated room. During each session they were sequentially presented with tuna fish, Purina cat chow, a live rat, a passive but otherwise normal male cat (or an anesthetized male), and finally the dominant male of the entire cat colony. A trained observer tape-recorded a running commentary throughout these sessions, utilizing standard terminology for behavioral ratings together with a free-flowing narrative description of the behavior. The commentary was later scored for relevant behavioral variables.

After a base-line or adaptation period, PCPA suspended in a neutral citric acid–phosphate buffer was administered subcutaneously each day to the cats. The daily dose for cats in group A was 150 mg/kg whereas the dose for cats in group B ranged between 75 and 300 mg/kg. The cats in group A had six to nine 1-hour-long observation periods during the first 9 days of PCPA treatment. The number of observation sessions ranged between 3 and 32 per cat for the combined groups. The PCPA treatment periods were 5 to 37 days. In addition to the standard observation sessions, notations were made by all laboratory personnel whenever appropriate throughout the day and night.

Pronounced changes in behavior developed rapidly in every one of the experimental animals after a latency of 3 to 5 days from the initial injection. These changes did not appear to be modified by the variation in PCPA dosage among the group B animals. Of the constellation of emergent behavioral changes, the appearance of "hypersexuality" was perhaps the most dramatic. By "hypersexuality," we mean the marked tendency of one male cat to mount and attempt intercourse with another male cat (*5*). Although homosexual behavior has been occasionally reported in presumably normal cats (*6*), under the conditions prevailing in our laboratories over the past several years countless opportunities for such interactions among male cats have produced only one or two undocumented instances of mounting. These many opportunities have included specific test situations similar to those used in the study reported here (*7*).

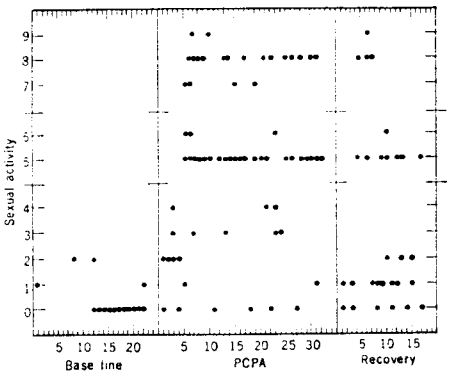


Fig. 1. The daily sexual activity of one cat observed before, during, and after PCPA administration. The abscissa is divided into days. Scoring categories for sexual behavior are represented by the following numbers on the ordinate: 0, not observed for sexual activity; 1, no interaction, ignores other cat; 2, sniffs other cat casually; 3, grooms its own genitals; 4, grooms other cat anywhere; 5, makes a sexual cry; 6 pursues other cat, sniffing it; 7, tries to mount but is easily discouraged; 8, mounts in an integrated deliberate manner; and 9, mounts reflexly, almost involuntarily, in a stereotyped fashion. Categories 1 to 4 are normal patterns of behavior among cats; 5 and 6 are preliminary sexual maneuvers; and 7 to 9 are overt sexual acts. Category 10 (will fight to mount or stay mounted) was not seen in this cat. On some days more than one observation was made.

There is a fairly definite and easily graded sequence of behaviors which constitute a complete sexual act for the cat (see Fig. 1). For the sake of simplicity, we have divided the sequence into preliminary maneuvers (sniffing, pursuing, vocalizations) and complete mounts (mounting though easily discouraged, persistent mounting, disorganized mounting). Only one instance of complete mounting was seen during the 78 base-line sessions with cats of group A. After administration of PCPA, 10 of the 13 cats in group A spontaneously mounted other male cats in a total of 52 out of 128 encounters during the test situation. Seven cats from group B were exposed to other male cats after PCPA treatment either during test situations or by chance. Five of these animals were observed to execute complete mounts. The time course of the development of hypersexuality depicted in Fig. 1 is representative of all the cats. Soon after PCPA treatment was initiated, there was an increase in preliminary maneuvers ($P < .02$), culminating in complete mounts between day 3 and day 6 after the start of the drug treatment. Many of the observation sessions during PCPA treatment in which mounting was not seen occurred in the first days of drug administration.

An equally impressive change in rage behavior also occurred. As one test of this, a large laboratory rat was routinely released in the observation room with group A animals. Only one cat attacked and killed rats before the drug was given. During the period of drug treatment, however, in repeated instances 6 of the 13 cats killed rats. As the treatment period progressed, the attacks became more confused and

savage, and the cats would bat and tear at the rat, then gnaw on it, and, if allowed, eat it completely. In several years of utilizing rat-cat interactions as a test of aggression, we had never seen a cat eat a rat after killing it. Although most animals became much more vicious when subjected to PCPA treatment (several cats actually attacked and severely mauled experienced technicians—not to mention other cats—entirely without provocation), a few unpredictably became more affectionate and would even prefer rubbing against the observer's legs to eating tuna fish.

A third category of changes seemed to involve perceptual processes. Their complexity and individuality resisted simple description and quantification. Every animal receiving PCPA showed a variety of perceptual disturbances, the development of which was consistently related to the time course of the drug. In general the first change was an episode of prolonged wakefulness which usually occurred at around 50 to 60 hours after the first PCPA injection. The animals moved around restlessly in their cages, and even when they were crouched in one place they constantly shifted their weight from one side to the other. In the observation room they ceaselessly explored, sniffing and looking at each object many times. After this period of hyperactivity was well established, episodes of unusual perceptual behavior began to occur. At first the animals seemed to overreact to slight noises, and occasionally they looked wildly around the room when a single moving stimulus such as a rat was present. They often stared at a fixed point for long intervals. Eventually all of the cats showed episodes of looking around the room as though they were watching some obscure object moving in the air. Precautions were taken to assure that the cats were not, in fact, watching something real (for example, a fly). Rapid darting eye movements, orienting movements of the ears, and extensive sniffing often accompanied this visual searching. The extreme of these perceptual disturbances was seen in two-thirds of the cases when animals appeared to interact emotionally with stimuli not apparent to the observer. The animals were observed to hiss and back into a corner in a typical fear response, to strike out at unseen objects, and even to interrupt ongoing activity such as mounting another animal to attend to nonexistent stimuli.

It has been shown that the insomnia associated with PCPA treatment in cats can be markedly reduced by administration of the serotonin precursor 5-hydroxytryptophan (5-HTP) (*3*, *8*). Two animals were given single injections of the precursor in very small dosage (1 mg/kg). As a result there was a definite reduction of abnormal behavior in the waking state (that is, the animals did not mount, kill rats, or exhibit other aggressive behavior). After about 8 hours abnormal behavior returned to its level before treatment with 5-HTP.

After 5 or 6 days of PCPA administration the intensity of the behavioral changes appeared to diminish in most cats. This was much more true of spontaneous behavior such as eating, drinking, grooming, and pacing than of elicited behavior. Thus after ten or more days on PCPA a cat might just sit if left alone but would still become violently enraged from a pinch on the tail and would still mount if presented with another male cat.

Thirteen of the animals in this study, and, in addition, nine animals who were not undergoing behavioral testing, were killed and perfused with saline for biochemical analysis of brain tissue. Serotonin was assayed fluorimetrically with tissue extraction either by solvent extraction with butanol or by ion-exchange chromatography with Bio-Rex 70 (a weakly acidic resin containing carboxylic acid exchange groups). The fluorescence assay was performed after the addition of hydrochloric acid, and similar results were obtained with both procedures (*9*).

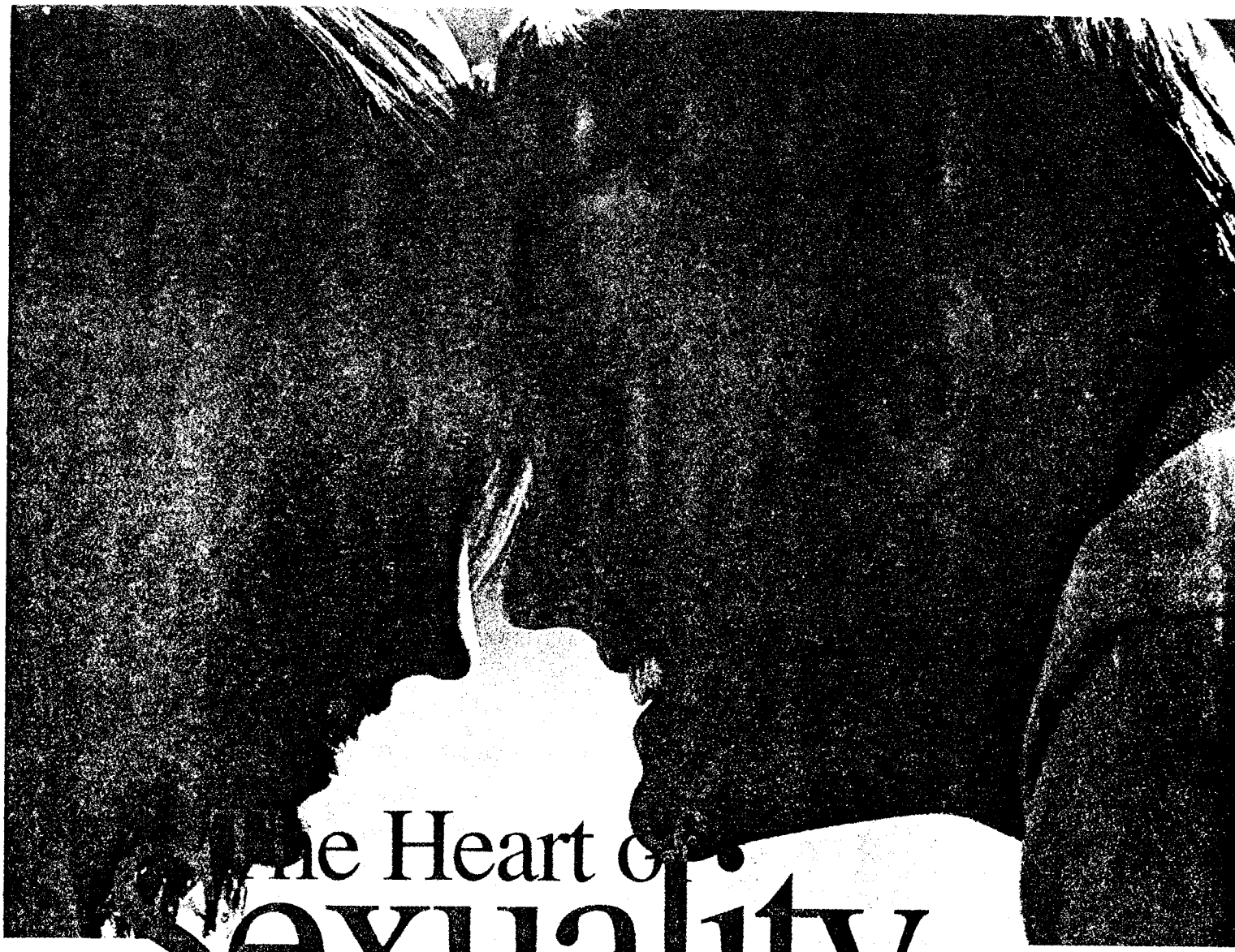
The concentrations of serotonin in the brainstems of cats ($N = 3$) that were treated with PCPA for 5 days at a daily dose of 150 mg/kg changed from 0.65 μg/g in controls to 0.06 μg/g in experimental animals. After PCPA treatment for 9 days the concentration of brainstem serotonin was 0.03 μg/g ($N = 5$). Single animals killed at various times thereafter up to 37 days of treatment showed similar low concentrations of brainstem serotonin.

Eight cats were studied during the period of recovery from the drug treatment (*10*). Fifteen days after treatment with PCPA was discontinued, this group of animals no longer exhibited unusual behavior patterns. Although systematic observations were not continued beyond this point, we felt that the animals' subsequent behavior was essentially normal.

Nearly all the cats studied showed marked alterations in sexual, aggressive, and perceptual behaviors during chronic administration of PCPA, and all animals were definitely changed by the drug in one or more of these categories of behavior. In addition, all animals suffered a reduction in total amount of sleep (*11*). These findings of totally altered behavioral patterns in cats are in marked contrast with the paucity of behavioral consequences of PCPA treatment reported in earlier investigations (*2*, *3*). However, a recent report on the effects of PCPA in rats has documented simultaneous enhancement of sexual, aggressive, and grooming behaviors (*12*). Augmentation of sexual behavior in rats treated with PCPA has been confirmed (*13*), and incidental observation of mouse-killing tendencies in rats treated with PCPA presumably confirms the enhancement of aggressive behavior (*14*).

In all of this work it would appear that the behavioral response to PCPA administration is more intense and more enduring and involves more specific modalities of behavior in the cat than in the rat. The same applies to the effect of PCPA on sleep patterns in the rat where the reported changes range from moderate changes to none at all (*15*). However, before one concludes that a profound and encompassing behavioral effect of PCPA administration is unique to the cat, further studies with long-term administration of PCPA at several concentrations and continuous observation of many behavioral modalities in the rat should be done. It is possible that discrepancies in the response to PCPA across species would be reflected in differential changes in other compounds during PCPA administration (*16*).

It is worth noting that the behavioral changes associated with long-term PCPA administration are provocatively similar to the changes associated with prolonged selective deprivation of rapid eye movement (REM) sleep in both cats (*7*, *17*) and rats (*18*), although the effects of the manipulation of REM sleep are somewhat less intense. Furthermore, the administration of amphetamine to rats deprived of REM sleep intensifies the syndrome to the point where compulsive mounting and aggressive posturing occur spontaneously (*19*). Finally, the above-mentioned behavior of rats given amphetamine and deprived of REM sleep is identical with the behavior of rats who



The Heart of Sexuality for Men and Women

By Linda Page, N.D., Ph.D.

I believe sexual intimacy with a loving partner brings nurturing, healing energy into our lives and connects us with the divine. We must remember, though, that great sex depends on good health. In fact, virtually every gland plays a part in the release and function of sexual response—all connected through direct or indirect exchanges with the hypothalamus. Needless to say, any imbalances from stress, fatigue, or a poor diet that adversely affect the way the hypothalamus functions will have a debilitating, detrimental, even destructive impact on sexual response!

Men and women are from the same planet. But our bodies have specific needs when it comes to sex. Let's start with men.

The male libido

A man's sex drive and function is largely dependent upon testosterone, sensory stimulation and a good blood supply to the erectile tissues, factors that rely on adequate nutrition and exercise! Men break down tissue; they expend energy, as in the discharge during sex. They need denser foods, more concentrated proteins and three times the volume of complex carbohydrates as women.

Foods that enhance male sexuality include zinc-rich liver, oysters, nuts, seeds and legumes, seafood, root vegetables, organ meats, and whole grains. Other nutrients for male sexuality include essential fatty acids like those in evening primrose oil, and vitamins A, B-6, and E.

Fava beans are rich in L-dopa, an amino acid that increases dopamine levels. Dopamine is intimately associated with sex drive in men.

Exercise! Most men have no idea how closely regular exercise is linked to their sexual performance. Studies show that men who exercise for 60 minutes three days a week have significantly enhanced sexuality, including increased frequency, performance and satisfaction.

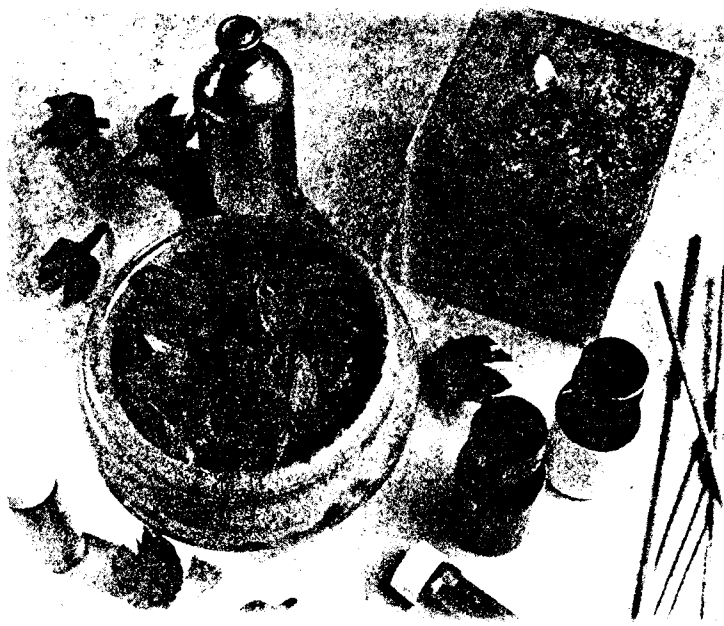
Sexuality-enhancing aromatherapy oils for men include cinnamon, sandalwood, lavender, patchouli, coriander, jasmine and cardamom.

Herbal helpers

The most sexually stimulating herbs contain substances that support male gland and nerve systems in a direct way. Bear in mind that a combination of herbs always works better than any one single herb.

- Yohimbe bark increases libido. A normal dose of yohimbe is 750-1000 mg. Avoid if you have high blood pressure, schizophrenia, heart, kidney or liver disorders, or if taking decongestants or diet aids containing phenylpropanolamine.
- Potency wood (muira pauma), a powerful aphrodisiac herb from South America, helps stimulate male libido and overcome erectile dysfunction.
- Ginkgo biloba is extremely beneficial in the treatment of erectile dysfunction caused by lack of blood flow to the penis.
- Saw palmetto is a natural steroid source herb and is a primary herb for male impotence, low libido, tonifying the male reproductive system and prostate health.
- Ginseng—I have worked with ginseng for years as a sexual enhancer. Ginseng can be a man's best friend for a body that is stressed or exhausted. Its best effects do not develop instantaneously but rather build up, as deep level balance and healthy sexual function are restored over time. However, many men do use ginseng for quick, on-call energy. Larger doses of four to six capsules daily for one to two months are effective for more intense stimulation.

Panax ginseng is a proven source of plant testosterone that can help normalize a man's sexual hormone supply. While continued use of concentrated panax ginseng may not be advisable over a long period of time, one to two capsules of a ginseng combination may be taken over many months for long-term revitalization.



Art of aromatherapy

Sexuality-enhancing aromatherapy oils for men include cinnamon, sandalwood, lavender, patchouli, coriander, jasmine and cardamom. Use only one oil at a time. Add one drop to water in a special aromatherapy burner. Sexuality-enhancing aromatherapy oils for women include ylang ylang, rose, clary sage, neroli and rosewood.

A woman's sexuality

For women, it all comes down to hormones. They are the basis for all metabolic activity. Even in the tiniest amounts, they have, as any woman can tell you, dramatic effects.

Women build up tissue; they receive energy, then convert and enrich it to create life. They need less protein than men, and a smaller volume of complex carbohydrates for conception and fertility. Nutrition is important for female sexual function, especially as a woman approaches menopause, when estrogen levels change.

Soy foods and plant hormone rich herbs are important. In

a recent test, women who consumed the equivalent of one cup of cooked soybeans daily showed an increase in the number of cells lining the vaginal walls, offsetting vaginal drying and irritation.

Foods that enhance female sexuality include fennel, celery, parsley, high-lignan flaxseed oil and seeds. The newest studies indicate that zinc-rich foods also increase sexual function in women. And foods with vitamin E such as soy foods, wheat germ, seeds, nuts and vegetable oils are very important. Naturopathic doctors have used vitamin E for years to reduce vaginal dryness and increase post-menopausal libido.

An essential mineral

Studies on post-menopausal women show supplemental daily boron results in elevated estrogen levels that are the same as the levels found in women on estrogen replacement therapy. Green leafy veggies, fruits (except citrus), nuts and legumes all have boron. If you take a boron supplement, be careful; too much boron can increase the risk of osteoporosis. About 3 mg. is a good daily dose.

Herbs for women

Herbs with aphrodisiac properties for women work differently than those for men. Their activity is rather to nourish and tone the female glands and organs rather than exert drug-like activity. Action is much deeper in the body, slower, gentler and longer-lasting, almost like the sexual experience itself.

• Ashwagandha is an Ayurvedic herb with ginseng-like activity that works well for women because it is a gentle energizer, less overheating and aggressive than panax ginseng, and well-suited to a woman's needs. It helps increase female sexual energy without overstimulating.

• Dong quai restores a women to hormone harmony. Often called the female ginseng because it acts as an adaptogen to maintain a woman's proper deep body balance, the Chinese consider it to be the queen of all female herbs.

• Damiana is a mild aphrodisiac and tonic for the central nervous and hormonal systems, and is a specific in compounds to treat frigidity in women.

• Siberian ginseng helps restore a woman's body balance, both physically and biochemically. It is often considered more suitable for women than panax ginseng because it modulates hormone release. Note: Siberian ginseng can be too stimulating for some women, so I recommend taking it for 14 days, then resting for 14 days before repeating.

I think that one of the best ways to use herbs as aphrodisiacs is to take them every day for a week before a romantic weekend.

Recipe for romance

I think that one of the best ways to use herbs as aphrodisiacs is to take them every day for a week before a romantic weekend. Here are some ideas to enhance romance!

• Burn a scented candle; vanilla, spice, bayberry or pumpkin are good choices.

• Eat lightly—perhaps an oyster and a seafood appetizer.

• Enjoy a little wine.

• Take 1-2 cayenne/ginger capsules.

• Play light music.

• Pour a couple of drops of aromatherapy oil into the tub—lavender is a good choice for relaxation.

• Sprinkle rose petals on the water.

• Make a special massage oil—add one or two drops of sandalwood oil into almond oil.

• Put a drop of ylang ylang oil on the pillow.

• Decorate with a fresh rose with a ribbon and fancy mints on the pillows.

In my own experience of working with herbs and men and women for more than 25 years, I can frankly say that some herbs have undeniable qualities that can turn a couple's attention to love!

Linda Page, N.D., Ph.D., is a well-known teacher, lecturer and author. She has appeared on more than 500 radio and television shows and has a new PBS show: The World of Healthy Healing—Unleashing the Healing Power of Herbs. *A practicing herbalist, she has formulated many proprietary formulas for men and women. For additional information, call (888) 447-2939 or on-line at www.healthyhealing.com* ©*Traditional Healing, Inc.*

DISCOVERY JULY '91

Medicine

UPLIFTING PILL

The path of drug development is seldom straight and narrow. Unanticipated side effects, for example, can be worse than the cure, or they can be therapeutically useful. Both happened with a drug called trazodone.

In the early 1980s a few hundred men who took trazodone for depression were in for a big surprise. They had unexpected erections or unusually prolonged and painful ones. In a few cases only surgery could make the erection go down. But such surgery can cause impotence, and lawsuits were brought against the drug's manufacturer, Bristol-Myers. To assess the drug's side effects, the company funded a study that was published in January. Tests on six healthy men were conducted at night to take advantage of the fact that the average male experiences four 45-minute erections during a typical night's sleep. When the men took trazodone, they had erections for an average of four hours—an hour longer than when they took a different antidepressant or a look-alike placebo.

"That makes trazodone the first oral drug that's been proved to prolong erections," says the study's leader, Irwin Goldstein, a urologist at Boston University School of Medicine. In a normal erection, he explains, small arteries that bring blood to the penis dilate, and the organ's muscles relax, allowing more blood into its spongy chambers. As the chambers swell they compress the outer veins that usually drain blood from the penis, keeping it engorged. The erection ends when nerve signals tell the muscles and arteries to tighten again, decreasing circulation to the penis. Trazodone appears to block these signals, causing the erection to persist.

For an antidepressant such a trait might be a liability. But it would be welcomed by the million mildly impotent American men whose penis-filling arteries are narrowed by atherosclerosis or injury. These men take longer to achieve erections, a problem compounded by their frustration, which triggers nerve signals to drain the penis. "A safe form of trazodone," says Goldstein, "would prevent patients from turning themselves off." Certainly a pill would be easier to swallow than current options such as erection-enhancing injections, painful vacuum devices, and hydraulic penile implants.

In its present form, though, trazodone isn't the answer. "One man in the study had an erection all night, which is sort of scary," notes Goldstein. The next step, he says, is to isolate the molecule in trazodone that causes erections. But Bristol-Myers, which undertook the study because of its legal problems, doesn't want to take this step. "The study's intent, unfortunately, was not to improve the plight of the impotent man," says Goldstein. "I'm hoping that someone else will become interested in funding this."