

**Reproductive Biology**

# **GOSSYPOL**

**A Potential Contraceptive for Men**



**Edited by Sheldon J. Segal**

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# **GOSSYPOL**

**A Potential Contraceptive for Men**

This volume is dedicated to the researchers of China, who persevered for many years in studying gossypol, and who in so doing have made a substantial contribution to the field of male fertility regulation.



## PREFACE

The search for a reversible male contraceptive has centered upon the suppression of sperm production or sperm motility. Gossypol, a natural substance extracted from the cotton plant, appears to cause both of these effects. Its ability to reduce spermatogenesis in men is undeniable and has been demonstrated in both large studies in China and a smaller confirmatory study in Brazil. These investigations have revealed the remarkable fact that with gossypol, it is possible to separate an effect on the testis' gamete-producing function from an effect on its hormone-producing function. Thus, it is possible to maintain normal testosterone levels and libido while sperm counts (and motility) fall.

Because of this unique and important action, gossypol warrants the fullest possible evaluation as a potential male contraceptive.

Sheldon J. Segal

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Sheldon J. Segal

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## INTRODUCTION AND HISTORY OF GOSSYPOL

Whether one's perspective is directed toward the effects of high fertility on individual couples or to its impact on nations and the world community, reduced fertility levels are a desirable, even urgent, objective. Some degree of decline in the birth rate can be expected as a consequence of social progress. In many nations and subgroups within nations, however, high fertility itself retards social progress. If fertility could be reduced while other social developments are pursued, a multiplier effect would occur, thus accelerating the overall process. Many nations, particularly in the Third World, have instituted national programs to educate individuals about the personal benefits of fertility regulation and to provide greater access to existing contraceptive methods. Because existing technology has limitations, however, many countries also are encouraging research directed at new and improved techniques for fertility regulation.

These are complementary and, indeed, necessary components of a successful national program. A decline in the birth rate would be expected from a vigorous family planning program that effectively distributes currently available contraceptive technology. In addition, new methods would contribute to program success, particularly if they are better adapted to the circumstances of nations lacking sufficient health resources. More effective methods, which can be distributed simply and inexpensively, would increase the acceptability of family planning at any level of personal motivation toward fertility control.

Since the development of oral contraceptives for women, there have been efforts to identify suitable drugs for inhibition of male fertility. A variety of antimetabolic agents and steroid hormones are known to suppress the production of sperm by the testis. However, the antimetabolic agents cannot be seriously considered as potential contraceptives because of their general systemic toxicity. At appropriate dose levels, the various hormones, including estrogens, progestins, androgens, and antiandrogens, block the production of sperm, through interference with endocrinological mechanisms.

Estrogens are among the most potent agents for this purpose; but long-term administration of estrogens to men can cause breast enlargement, loss of libido, and an increase in thromboembolic disease. Nevertheless, limited clinical investigations are still being conducted in the hope that these problems can be minimized by using very low doses of estrogens combined with testosterone. The preliminary results of these clinical studies confirm the observation first made by researchers in the mid-1970s that suppression of sperm production can be achieved in the short-term without evident side effects [1, 2]. Any extensive development of this approach, however, is not likely because of the toxicity of estrogens in long-term administration.

Although progestins are less potent than estrogen in inhibiting spermatogenesis, they have been much more widely tested in men because there is no firm evidence linking them to an increased incidence of cardiovascular disease in men. Sperm production can indeed be suppressed using progestins supplemented with androgens. Normal plasma testosterone levels are maintained, and sperm production can be restored when treatment stops. Current research, continuing the efforts begun a decade ago [3, 4, 5], still seeks to identify effective hormonal combinations without unacceptable side effects in dosages to be administered as either monthly injections or daily pills. Success is still elusive.

Testosterone itself inhibits sperm production if given in sufficiently high doses. Frequent intramuscular injections are necessary, however, and there is concern about long-term health hazards, vascular problems in particular, because of the high doses required. In an attempt to reduce toxicity, researchers have done some work with orally active steroids less androgenic than testosterone [6, 7, 8, 9, 10, 11]. However, relatively high doses of the anabolic agents studied have been only partially effective [12].

It is precisely because all avenues to the development of a reversible male contraceptive seem blocked that interest in gossypol, a polyphenolic compound isolated from the seeds, stems, and roots of the cotton plant Gossypium sp., is so great. For more than 10 years, researchers in the Peoples Republic of China have been working on developing the substance into a male contraceptive. They have clinical experience with the agent [13], which has thus far been used by more than 10,000 men. There are now data on its efficacy as a contraceptive and on its toxicity - but much remains to be done to elucidate its mechanism of action, its safety, its reversibility, and the dose levels at which it achieves its effects. The research reported in this book aims to answer some of these questions. Meanwhile, a look at its recent history is of interest.

### The Discovery of Gossypol's Antifertility Property

In the late 1960's, people in many rural areas of China, including in Hubei and Hebei provinces, complained of fatigue and of burning of the face, extremities, and other exposed parts of the bodies. The farms in the areas raised cotton. The afflicted people could not work in the fields, but hid in the shade, lying on rocks to get cool. Local doctors were puzzled. The disease had reached epidemic proportions, but the cause remained unknown. The peasants called their disease "the burning fever" [14, 15].

Burning fever was especially prevalent in Xingtai, a county in Hebei province. A local doctor discovered that these affected peasants consumed raw, homemade, cotton seed oil. Commercially manufactured cotton seed oil had been used in cooking for many years, but only in the 1960's, did the peasants begin to make oil from uncooked seeds, using their own pressing machines. Raw cotton seeds contain gossypol which is destroyed by heat. Unlike the commercial process, preparation of homemade oil does not include heating. Consequently, gossypol remains dissolved in homemade oil. This substance was discovered to be the cause of the burning fever.

Gossypol was first discovered by J. J. Longmore in 1886 [16], and was purified in crystalline form by the Russian chemist, L. Marchlewski, in 1889 [17]. Researchers have often tried to make use of all parts of the cotton plant. The seeds contain protein and oil, and attempts have been made to adapt cotton meal as an animal feed and as infant food. However, the plant was found to be toxic and such attempts were not successful.

As soon as crude cotton seed oil was identified as the source of burning fever, Xingtai doctors advised their patients to stop pressing their own raw oil. The burning and fatigue stopped. Several years later however, many couples were found to be experiencing fertility problems. A large number of women had amenorrhea, and many men were impotent. These cases of infertility were regarded as a sequel of burning fever. When women remained on gossypol-free diets, many eventually recovered from amenorrhea. Very few men, despite the elimination of gossypol from their diets, recovered from their infertility and impotency. Further examination of these men revealed azoospermia or oligospermia. In addition, some men noted a decrease in testicular size. Medical and scientific research workers from universities and hospitals were sent to the area to investigate these problems. They confirmed the findings of the local doctors. Infertility was prevalent, and women seemed to recover at a much higher rate than men. Men who did recover were found to have consumed a lower total amount of cotton seed oil for shorter periods of time. This information led investigators to hypothesize whether controlled doses of purified gossypol could be used effectively as a male fertility-control agent. Observational studies in the

countryside had shown that burning fever, fatigue, and infertility were the most serious effects of gossypol ingestion. Mortality was not observed as a result of burning fever. Because the rate of recovery from male infertility was dependent on the amount of cotton oil a man had consumed, scientists conjectured that infertility would most likely be reversible if the gossypol dosage could be limited. Cessation of intake would probably lead to restoration of fertility.

#### Animal Studies Testing Gossypol for its Effectiveness and Toxicity

Researchers began animal experiments in the late 1960s and studies using male rats, mice, rabbits, hamsters, dogs, and monkeys yielded almost identical infertility results [18]. In addition, the absorption, distribution, and excretion of gossypol were also found to be similar in these animals [19].

The biological half-life of gossypol in the gastrointestinal tract of the rat is about 10 hours. Elimination of gossypol takes place mainly through the bile-fecal pathway, while excretion through the kidney is minimal [20]. Its elimination from the body is slow, taking a rat 19 days to eliminate 97% of the dose from its body [21]. Continued administration, therefore could lead to accumulation.

The half-life of gossypol in mice and dogs is longer than in rats [22]. This might explain the more obvious toxic reactions in the former two species. Dogs are more sensitive to the toxic action of gossypol. They are more likely to die as a result of anorexia and of pulmonary and myocardial disturbances. Monkeys, however, exhibit few adverse reactions at the antifertility dosage [23, 24].

The order of gossypol distribution throughout the body in all animals studied is liver, gastrointestinal tract, spleen, lymph nodes, kidneys, heart, lungs, pancreas, salivary glands, muscle, adipose tissue, testes, blood, urinary bladder, brain and spinal cord [25]. Although the testes do not retain much gossypol, sperm cells are vulnerable to the substance. Because gossypol concentration is high in the liver and kidneys, there should be special concern about toxic effects on these organs.

Research carried on during the 1970s helped elucidate many aspects of the mechanism of action of gossypol, its effects on endocrine function, on the various reproductive structures, on its toxicity and on its antifertility effects in a wide variety of animals including mice, rats, hamsters, rabbits, bulls, and monkeys. Its effects on human males was also studied closely by Chinese investigators and was reported at numerous conferences and in scientific journals.

Research continues today in laboratories around the world. This book presents an up-to-date report on many facets of gossypol research. The findings, considered with earlier results, suggest that while much remains to be learned, gossypol is still a promising male antifertility lead. Its antifertility properties have been confirmed. It is now fairly certain that it acts locally, at the level of the reproductive organs themselves, and does not interfere with testicular hormone production. During the first few weeks of treatment, gossypol attaches to maturing sperm stored in the epididymis and renders them immotile. In the course of longer treatment, the drug also acts in the testes to check sperm production. These characteristics, the direct action on the motility of mature spermatozoa and on the growth of immature sperm cells is what sets gossypol apart from other potential chemical fertility-regulating agents. Gossypol acts without interfering with the Leydig cells or with the pituitary-gonadal system. Therefore, it should not affect a man's sex drive and should not disturb the general hormonal regulatory system. Research reported here is also reassuring on the issue of the drug's possible teratogenic effects.

All of this is not to say that gossypol is without disadvantages. Optimism must be tempered. The risks of sterility and hypokalemia, as well as possible toxic effects on the heart and liver, cannot be ignored. Nor should they be exaggerated, however. One should remain aware of the results of animal experiments using dogs and other sensitive species, keeping in mind that still other animal species, especially primates, exhibit a much lower toxic reaction and require a lower antifertility dose. Nonetheless, toxicity remains an issue of concern.

Clearly, much more study is required. Nonetheless it is important to recognize that gossypol is a major and promising lead in the search for a safe, effective, reversible, and inexpensive fertility-regulating agent.

Guo-zhen Liu and Sheldon J. Segal

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