5-Thio-D-Glucose: A Unique Male Contraceptive

Testes and some tumors, surprisingly, share an unusual characteristic: Their utilization of sugar differs from that of other bodily tissues. The ability of testes to produce sperm, for example, seems to be directly related to the amount of D-glucose that can be absorbed by testicular cells. Some tumors, as was discovered by Otto Warburg some 50 years ago, rely to an unusual extent on the inefficient, anaerobic degradation of D-glucose to release some of the energy it contains.

The biochemical bases for the two phenomena are still unknown, but it is conceivable that interference with the metabolism of D-glucose might provide a way to interfere with both spermatogenesis and tumorigenesis. New evidence suggests that this is just the case. Roy L. Whistler of Purdue University, West Lafayette, Indiana, recently told the national meeting of the American Chemical Society that a sulfur analog of D-glucose, 5-thio-D-glucose, acts in just such a manner in mice, and preliminary results indicate that it may be both an effective male contraceptive and, in some cases, an antitumor agent.

The demonstration that 5-thio-D-glucose inhibits spermatogenesis represents a major breakthrough in the field of male contraception. Most investigators have previously used either alkylating agents, which are toxic chemicals that react with dividing sperm cells to halt that division, or hormones to regulate spermatogenesis. The alkylating agents have been largely unsuccessful because they also react with other dividing cells within the body to produce undesirable side effects. Hormonal manipulation has been more successful, but it has also presented problems because of interference with the libido and the difficulties of finding the proper agent to render nearly all subjects infertile.

Perhaps the best results with hormones have been obtained by C. Alvin Paulsen of the University of Washington, Seattle. Paulsen uses a regimen that combines monthly injections of a potent hormone ester such as testosterone enanthate and daily doses of a weaker synthetic hormone analog named Danazol. He found that 23 of 37 men on such regimens produced fewer than 5 million sperm per ejaculation, the number normally associated with infertility. (Untreated men produce 100 million or more.) Other investigators have obtained similar results with different combinations of hormones, but none of the results can be considered sufficiently satisfactory to begin any large-scale clinical testing. Hormones might, moreover, be expected to produce side effects in many individuals who would use them, just as they do in women who are taking the pill.

The results of Whistler and his associates, John R. Zysk, Alfred A. Bushway, and William W. Carlton, are the first to show that a chemical other than a hormone or alkylating agent can interfere reversibly with spermatogenesis. There is, furthermore, ample evidence suggesting that interference with sugar utilization can inhibit spermatogenesis and that Whistler's approach is viable. Diabetic men have, for example, frequently been reported to exhibit an increased incidence of impotence, a decreased sperm count, an impaired motility of sperm, or atrophy of the germinal epithelium of the testes. Similar findings have been obtained in rats that have been rendered diabetic either chemically or by surgical removal of the pancreas.

5-Thio-D-glucose, first synthesized by Whistler some 8 years ago, is essentially nontoxic in animals; the LD_{50} in mice (the dose at which 50 percent of the mice are killed) is 14 grams per kilogram of body weight—the equivalent, he says, of more than a kilogram in man. About 90 to 95 percent of the thiosugar is excreted unchanged within 6 hours. At least part of the remainder, Whistler has found, competitively inhibits the active transport of D-glucose across cellular membranes (although some D-glucose does cross the membrane by passive diffusion).

Some of the thiosugar also enters the cell, where it is phosphorylated by cellular enzymes. The monophosphate thus formed is a potent inhibitor of phosphoglucomutase, one of the enzymes in the glycolytic pathway. The toxic effects of the thiosugar at high doses, Whistler suggests, might thus arise from a complete shutdown of glucose metabolism.

At somewhat lower dosages, in the range of 50 milligrams per kilogram or more, the thiosugar induces a diabetes-like condition in mice; that is, the concentration of sugar in the blood is increased and some of the sugar spills over into the urine. This effect is short-lived, but can be maintained with repetitive doses. At the lower end of this range, the thiosugar causes a slight increase in blood sugar concentrations that depresses the appetite of experimental animals. The thiosugar might thus also find some use in weight control.

At the lowest effective doses, about 33 milligrams per kilogram in mice, the only observable effect was atrophy of the testes and a complete inhibition of spermatogenesis. There was no reduction in the libido of mice fed the compound, but they could not impregnate females. Dissection of killed mice showed that there were no pathological changes in the testes. The effects also appeared to be completely reversible. In animals that consumed the thiosugar for 7 weeks, then returned to a normal diet, sperm production was reinitiated and testes weight returned to normal within 4 to 8 weeks. These mice were able to impregnate females, and the litters that resulted were of normal size and health, as were litters of two succeeding generations.

In less extensive experiments, Whistler and his associates have shown that the thiosugar is also an effective agent against malignant cultured cells. In tests with four different lines of tumor cells, they found that it not only inhibited division of the cells but also reduced their number by as much as 40 percent. Whistler says he hopes that other investigators will follow up on this discovery because he feels that he doesn't have the proper expertise for work with tumors.

Someone else may have to take up his work on the contraceptive activity also, since right now Whistler is out of funds. And much work remains, for his results are still only indicative. But it is almost a certainty that the work will be continued somewhere, for the results are simply too promising to be ignored.

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