

Progesterone in large amounts has immunosuppressive effect

The newest immunosuppressive drug to come on stage is progesterone, better known as the "essential hormone of pregnancy."

A team from the University of California, San Francisco (UCSF), School of Medicine has carried out studies showing that progesterone probably plays a critical role in preventing rejection of the fetus by the mother. The reason why this apparently had not been realized before is that the hormone was not investigated in high enough concentrations.

Pentti K. Siiteri, PhD, professor of obstetrics and gynecology and codirector of the university's reproductive endocrinology center, told the Endocrine Society meeting in San Francisco that in concentrations as high as those found in the human placenta— $2\mu\text{g/gm}$ to $10\mu\text{g/gm}$ —progesterone can block the rejection of cross-species skin transplants and can inhibit the mixed lymphocyte reaction. The latter is an in vitro test of the ability of T lymphocytes to recognize foreign antigens and respond to the challenge by increasing cell division.

Immunologic tolerance of pregnancy has always been a puzzle, and various investigations have chipped away at the answers through the years. One possible explanation has been immunologic enhancement, that is, the coating of fetal cells by maternal antibodies that then protect them from destruction by the mother's cell-mediated immune system (*JAMA MEDICAL NEWS* 217:1309 [Sept 6] 1971). Other theories have ascribed protection to nonantigenicity of the trophoblastic cells, to trophoblastic secretions that mask fetal histocompatibility antigens, or to suppression of cellular and humoral immunity by trophoblastic hormones.

Still another theory, with a good deal of support, has been that placental hormones—human chorionic gonadotropin (HCG), human chorionic somatotropin (HCS), progesterone, and the estrogens—may play an important role in preventing fetal rejection. One of these, HCG, stirred up a good deal of interest for awhile because somewhat crude HCG preparations

appeared to inhibit the mixed lymphocyte reaction. Later, however, when more pure preparations were obtained, the inhibitory activity was lost.

"Our position on HCG now," said Louis E. Clemens, PhD, one of Dr Siiteri's co-workers and a postdoctoral fellow in obstetrics/gynecology, "is that it has no direct effect on cell-mediated immunity. However, since HCG is a gonadotropin, it may be stimulating the production of progesterone and estrogens and thus have an indirect role in preventing fetal rejection."

Progesterone had been studied previously for its immunosuppressive capabilities, Dr Siiteri said. For example, it was experimentally administered to animals systemically to see whether it could prevent rejection of a skin graft. However, its effects were negligible—probably because it has a rather short

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Melanie is one of the pupils at a very special nursery school in Kansas City, Mo, that is described in a story beginning on page 907. Riding the tricycle (specially designed for partially paralyzed children) helps to improve mobilization and coordination.

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half-life in the bloodstream. The San Francisco workers, realizing that the concentration of progesterone in the pregnant uterus is very high (it is produced by the corpus luteum during the first trimester and by the placenta during the last two trimesters), then decided to reinvestigate the possibility that progesterone has an important immunosuppressive role.

In a series of experiments with rats, progesterone was placed inside tubes made of porous Silastic so that it could easily diffuse to the outside. The tubes were wrapped with antigenic substances—either cotton thread or hamster skin—and placed in the flanks of female rats. Control implants contained either nothing or other steroids like estrogen.

"The response was astounding," Dr Siiteri said. An inflammatory response consisting of the proliferation of granulomatous tissue and adhesions appeared within a week in the control implants. The experimental implants elicited almost no inflammatory response.

In the hamster skin-wrapped implants, complete destruction of skin in the controls occurred within eight to ten days. All the implants containing progesterone survived for more than two weeks and some up to 35 or 40 days.

The investigators also experimented with the Progestasert—an intrauterine device that contains progesterone (*JAMA MEDICAL NEWS* 235:2378 [May 31] 1976). The release rate of progesterone from this device is 1/30th that of the progesterone in the Silastic tubes, but it still delayed rejection of the foreign skin in the experimental animals.

The next series of experiments involved the ability of progesterone to inhibit the human mixed lymphocyte reaction. "At levels comparable to those found in the human placenta, the progesterone exerted significant suppression and inhibition," Dr Siiteri said.

"Thus, we believe that the local high concentration of progesterone in the human placenta is part of the reason that the fetus is not rejected. The concentration is considerably diluted in the mother's general circulation, allowing her to maintain normal immunologic responsiveness."

Other factors are probably involved, he added, such as glucocorticoids that circulate in the mother's body during pregnancy, factors in pregnancy serum that block the mixed lymphocyte reaction, and HCG. "It may be that HCG coats the fetal cells and so helps to prevent rejection early in pregnancy (it peaks at 60 to 80 days after conception and then drops) while progesterone takes on this role locally later on," he suggested.

"The effect is probably mediated at the level of the T lymphocytes and the activity of progesterone in high concentrations appears similar to that of the glucocorticoid hormones in achieving immunosuppres-

sion," Dr Siiteri said. He is studying the mechanism in collaboration with Daniel Stites, MD, assistant professor of medicine at UCSF, and director of the immunology center.

"Attempts to forestall abortion in women by giving progesterone or synthetic derivatives over the past 20 years have met with limited success," Dr Siiteri explained at a press conference. "This likely is due to the difficulty in achieving the high levels normally present in the uterus when drugs are administered systemically. New solutions to this problem may help reduce premature birth."

The implications of these findings for transplantation immunology and cancer therapy may be considerable as well, he indicated. There is preliminary evidence that some cancers produce progesterone.

In addition to Drs Clemens and Stites, other investigators involved in the studies were Freddy Febres, MD, and R. Jeffrey Chang, MD, both postdoctoral fellows in obstetrics/gynecology, and Bernard Gondos, MD, associate professor of pathology.

Background radiation level lies near 'danger' mark

A gradual realization is emerging, says a laser expert, "that ambient levels of ultraviolet, infrared, and visible radiation in man's natural environment are not so far below hazardous levels as once was thought."

In fact, we are normally living fairly close to the danger point, according to David H. Sliney, MS, chief of the Laser Branch, US Army Environmental Hygiene Agency, Aberdeen, Md, in a report to the Research to Prevent Blindness foundation seminar in Reston, Va.

Mr Sliney told the seminar that "in fact, ambient levels are very close to the borderline for creating adverse effects to the eye upon chronic exposure. Ultraviolet radiation in sunlight may be a major factor in senile cataract. It also has been argued that exposure to bright light accelerates the retinal degeneration of retinitis pigmentosa. In industrial processes such as welding and material processing, worker's eyes sometimes are exposed to hazardous levels of optical radiation. . . ."

Much of the increased study of optical radiation effects on the eye in the past ten years was prompted by concern about laser safety, Mr Sliney says (*Archives of Environmental Health* April 1975).

