therapy reported on the outcome of such management in 36 women over an eight-year period.

Irradiation of the pituitary gland induces gradual shrinkage of the tumor over several years, the British investigators noted. Since this treatment acts slowly to lower hormone levels, they administered bromocriptine in the interim. All patients were initially treated with megavoltage radiotherapy over a period of six weeks and were followed at regular intervals thereafter. Of those women who wished to become pregnant, 73% succeeded, usually within two months of attempting conception. Bromocriptine was stopped at confirmation of pregnancy.

"When tested off bromocriptine," the British group reported, "all but two patients showed a fall in serum prolactin, which appeared progressive with time. Serum prolactin had become normal in 25% of the total patient group at the time of last assessment.... We conclude that the combination of radiotherapy and bromocriptine is a safe and effective treatment for prolactinomas and is highly successful in allowing safe conception and pregnancy. Prolactin levels progressively fall in the blood as a result of the radiotherapy."

Problems of infertility and sexual dysfunction in men were addressed by other investigators. In up to 50% of infertile couples, noted a group from Walter Reed Army Medical Center, the problem can be traced to the male partner.

Because it is often difficult to identify a specific cause of oligospermia, Drs. Robert A. Vigersky and A. R. Glass, of the Kyle Metabolic Unit, applied a working hypothesis: Since the testicles of all normal men produce small amounts of estrogens, "low sperm counts might be caused by slight increases in this estrogen production or by an increased effect of normal amounts of estrogen."

They tested this hypothesis by treating oligospermic men with drugs that would decrease the amount of estrogen and increase the ratio of androgen to estrogen. Their initial study showed that testolactone, a drug that inhibits estrogen production, markedly improved sperm counts in infertile men with oligospermia of undetermined etiology. More recently, they added tamoxifen to the testolactone regimen in 15 oligospermic men. (Tamoxifen, which blocks the ability of estrogen to act on the body's tissues, is used for estrogen-receptor blockade in chemotherapy of estrogen-dependent breast cancer.) The combined treatment was similarly effective, the investigators reported, suggesting that "reduction of estrogens may be a useful approach in treating infertile men with low sperm counts."

Erectile dysfunction in nondiabetic older men was the subject of investigation at a special clinic at the Sepulveda VA Medical Center in Los Angeles. The most common coexisting problems noted in 42 impotent men over 50 were hypertension (50%), atherosclerosis (48%), use of medications that can cause sexual disorders (57%), prior vasectomies (33%), and prior prostatectomies (21%).

"The high incidence of prior vasectomy was completely unexpected," reported Drs. Susan Stanik, Sharon P. Viosca, Clara Windsor, and colleagues from the department of medicine of the UCLA–San Fernando Valley Program. "Even more striking was the fact that many of the patients had their vasectomies 20 or more years previously, when very few such operations were being carried out." The association, although noted in a small sample, was viewed as "highly significant," and, "for the first time, throws a shadow of doubt on the long-term consequences of vasectomy."

Smallpox Conquered, Vaccinia Directed Against Hepatitis B

A recombinant live virus vaccine that stimulates protective antibodies against hepatitis B in animals has been developed by scientists at the National Institute of Allergy and Infectious Diseases, NIH. Rabbits injected with the hybrid vaccinia virus containing the gene for hepatitis B surface antigen (HBsAg) produced levels of antibody to hepatitis antigen that were higher than those required to provide protection in man.

This triumph of recombinant DNA technology, reported in Nature (302:490), may have worldwide implications for mass immunization against hepatitis B, according to the authors, Drs. Geoffrey L. Smith, Michael Mackett, and Bernard Moss. Approximately 200 million people are chronically infected with hepatitis B, they pointed out, noting that "large numbers of deaths are attributed to fulminant hepatitis, cirrhosis, and primary hepatocellular carcinoma." This new type of recombinant virus offers promise for use as a less costly and more easily administered vaccine than the currently available alternative.

The campaign to eradicate smallpox has been the most successful mass vaccination program carried out in undeveloped countries, the NIH investigators noted in their report. They attributed the efficacy of this undertaking to such factors as "the potency, stability, and low cost of the live vaccine" and "the ability of medically unskilled per-

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Construction of chimeric vaccinia hepatitis plasmid, in which the coding sequence for HBsAg was inserted into the vaccinia virus next to a vaccinia promoter, is schematized. The hybrid virus grew well in cultures; recloned recombinants could be identified and recovered for use as vaccine in rabbit studies.

sonnel to administer it in nonsterile conditions as a single dose on a mass scale.”

The smallpox experience encouraged the NIH group to pursue the development of “a vaccinia virus recombinant hepatitis B vaccine for immunization in areas where the risks of hepatitis greatly outweigh the low incidence of side effects of vaccination…. The feasibility of constructing such chimera was demonstrated by the molecular cloning and expression of the herpesvirus thymidine kinase gene in vaccinia virus.”

The investigators described in detail the strategy utilized for inserting the coding sequence for HBsAg into the vaccinia virus genome without loss of infectivity. To clone and express foreign DNA in vaccinia virus, they took into account the “large genome size and transcriptional regulatory signals used by the viral RNA polymerase. A chimeric gene consisting of a vaccinia virus promoter fused to a foreign protein coding sequence was flanked by vaccinia virus DNA within a plasmid vector.” These plasmids were constructed to “enable any continuous protein coding sequence to be inserted next to a vaccinia promoter.”

The hybrid virus grew well in cell cultures, releasing hepatitis B virus agglutinin in a form indistinguishable from the native antigen found in the serum of human carriers. The polypeptide encoded by the foreign DNA is produced during the growth cycle of the virus; recloned recombinants containing the HBsAg coding sequences could be identified and recovered from these cultures.

Two rabbits inoculated with the recombinant virus rapidly demonstrated typical local skin reactions and a significant antibody response to HBsAg. Within nine days of inoculation, the serum of both animals had anti-HBsAg titers of more than 200 mIU/ml; in one of the animals, the titer exceeded 2500 mIU/ml by day 31. Analysis of sera 94 days after vaccination indicated that anti-HBsAg titers had risen to 540 and 9600 mIU/ml in the same animals, respectively. “Although not directly comparable,” commented the investigators, “previous studies indicated that the minimal level of anti-HBsAg required for full protection of humans against hepatitis B virus infection was 10 mIU/ml.”

Long-term experiments to evaluate the safety and efficacy of this vaccine in susceptible chimpanzees have been initiated, the scientists reported. In addition, they suggested that preparation of polyvalent vaccines against a number of different pathogenic agents may be feasible.

In view of the success of their initial experiments, the authors suggest that the recombinant live vaccine might “offer advantages over alternative purified subunit vaccines that already or soon will exist.” Hepatitis B virus cannot be grown in tissue culture or in animals other than chimpanzees; moreover, the investigators pointed out, the absence of naturally occurring attenuated strains also has prevented development of a conventional live hepatitis B vaccine. The high cost of purification, safety testing, and multiple injections of the subunit vaccines currently used for high-risk groups in Europe and North America “pose problems for their widespread application in high endemic areas of Africa and Asia, where treatment of entire populations may be necessary.”

“Some difficult problems remain to be solved before this strategy can be adopted,” it was pointed out in a commentary accompanying the
Human Fetus Shown To Synthesize Bioactive HCG

A group of California investigators has demonstrated that the human fetus secretes human chorionic gonadotropin (HCG) in a form that is biologically active. Fetal synthesis of this hormone, previously thought to be produced only by the placenta, suggests that the fetus may participate in metabolic homeostasis during its development.

The study, reported in the April 15 issue of Science, was performed at the Department of Obstetrics, Gynecology, and Reproductive Sciences of the University of California at San Francisco by Drs. Robert W. Kuhn, W. Glenn McGregor, and Robert B. Jaffe, all members of the UCSF Reproductive Endocrinology Center.

High concentrations of HCG have (continued on page 42)