.01) than their noninjected counterparts. In contrast, they did not differ significantly from group 4-W or from the control group.

To clarify further the role of endogenous estrogen in concaveation-induced maternal behavior in the virgin animal, we used one additional group of 15 females (group 4-W + MER-25). These females were ovariectomized 4 weeks before testing, and during the last 4 days of the postoperative interval they were given daily injections of 50 mg of ethamoxytriphetol (MER-25), a drug that blocks the action of estrogen both centrally and peripherally (*5*). Our thinking was that MER-25 should reduce the effective levels of estrogen in the females ovariectomized for 4 weeks and consequently reduce the latency to maternal behavior. As expected, group 4-W + MER did not differ from group 8-W but did differ significantly from each of the remaining three groups ($P < .05$).

The adult male, like the virgin female, also responds to young if given an average of 5 or 6 days of continuous exposure. Because this concaveation-induced maternal behavior of males has also been considered free of endocrine influence on the basis of a postoperative interval of only 2 weeks (*3*), we investigated the possible inhibitory effects of testosterone. Males were tested 4 and 8 weeks after castration and compared with intact controls. In addition, steroid replacement was undertaken in 8-week castrates by giving daily injections of 0.5 mg of testosterone propionate during the last 7 days of the postoperative period. The results for males parallel those for virgin females (Table 1). Males 8 weeks after castration (group 8-W) had a significantly lower median latency to maternal behavior ($P < .01$) than did either intact controls or males 4 weeks after castration. Steroid replacement in males castrated for 8 weeks increased the median latency; these males did not differ significantly either from controls or animals castrated for 4 weeks ($P > .05$).

We have demonstrated that concaveation-induced maternal behavior in the rat is under endogenous steroid control and that this control is normally inhibitory in nature. Continuous stimulation by young can overcome the inhibition, but only after 5 to 6 days. Long-term removal of the gonads facilitates the inductive effects of concaveation, presumably by removing the suppressive action of testosterone and estrogen on the neuronal system mediating maternal behavior in the male and female, respectively.

The hormones accompanying the termination of pregnancy have been suggested as the agents responsible for the immediate responsivity of the puerperal female. Among these hormones is estrogen, which, when injected together with prolactin during progesterone withdrawal, facilitates the expression of maternal behavior in the ovariectomized virgin animal (*1*, *2*). The data reported here, in contrast, show estrogen to have an inhibitory influence. These results indicate that the particular behavioral effect exerted depends on the prevailing endocrine condition of the animal. Thus, in the virgin female subjected to high prolactin concentration and decreasing progesterone concentration (as normally occurs at the time of parturition), estrogen acts synergistically to facilitate the display of maternal behavior. On the other hand, in the normally cycling or ovariectomized female, each of which presents an hormonal picture different from that of the treated animal, estrogen inhibits the display of maternal behavior.

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Transformation of Cell Cultures Derived from Human Brains

Hooks *et al.* (*1*) describe transformation of cells in culture derived from a brain of a patient with Creutzfeldt-Jakob disease. These cells (henceforth referred to as "brain cells"), maintained in parallel with many other cultures of brain cells, began forming colonies, lost contact inhibition, and exhibited an aneuploid number of chromosomes. The authors failed to observe a similar transformation in the parallel cultures, or in any other cultures of human brain cells maintained in their laboratory. Although they detected a viruslike particle in these cells by electron microscopy, they were unable to "rescue" an infectious virus from these transformed cells. It appears unlikely from the authors' careful assessment of the conditions in their laboratory that this apparent transformation resulted from contamination of their cultures either by a virus, or by stray cells from some other tissue culture. They concluded that this transformation was indeed "spontaneous," but were unable as yet to relate this change to Creutzfeldt-Jakob disease.

Their report is the third of otherwise unrelated studies documenting transformation of human brain cells in culture. We observed this phenomenon (*2*) in two such cultures derived from patients with subacute sclerosing panencephalitis (SSPE). These two cell cultures, like the one reported by Hooks *et al.*, "spontaneously" lost their contact inhibition, began forming colonies, and displayed extensive chromosomal abnormalities, but retained their identity as human cells. In our laboratory, as in that of Hooks *et al.*, other human brain cultures failed to exhibit transformation.

Webb *et al.* (*3*) studied a human fetal brain culture deliberately infected with attenuated strain of measles virus and observed transformation of these cells, characterized by loss of contact inhibition and by colony formation. They were able to recover the original infectious virus from these transformed cells.

In view of the considerable divergence of these studies and conditions in the respective laboratories, as well as the different origin of the cells (SSPE, normal human fetal brain, and Creutzfeldt-Jakob disease) it appears that the only link among these three observations is the fact that the transformed cells were derived from human

brains. Yet it is highly unlikely that human brain cells, in marked contrast to human fibroblasts, have a capacity for "spontaneous" transformation. It may be therefore that they were transformed either by the disease agent—SSPE virus, measles virus, or the as yet unidentified agent of Creutzfeldt-Jakob disease—or that the transformation was related to some other, hitherto unknown, virus that was activated by the disease process. Neither of these possibilities can at present be established. However it is intriguing to speculate that human brain tissue may be a repository of a transforming agent. In progressive multifocal leukoencephalopathy, another progressive disease of central nervous system, two papova agents—one identical with SV40, an oncogenic DNA virus, and the other apparently different from it—have been isolated (*4*); and papovalike virions were seen by electron microscopy of brain cells cultured from a patient with SSPE (*5*). One may thus consider that papovaviruses, in some unknown manner, could have been involved in the transformation of the brain cell cultures.

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The SG transformed cell line we described, now in its 110th subculture, has been repeatedly examined by electron microscopy and continues to contain SG virus particles. We have not encountered evidence of papovavirus particles in these cultures; nor have we detected virus particles in more than 25 other human brain biopsies currently in culture. The failure to detect particles does not rule out the possibility of papovavirus-mediated transformation as noted by Katz *et al.* Technological improvements will be necessary to demonstrate any putative role of the papovavirus in transformation of human brain cultures.

In contrast to the explant cultures of human brain, those we have made from chimpanzees have usually yielded foamy viruses—specifically, one or both chimpanzee foamy viruses (Pan 1 and Pan 2) (*1*). Although these are viruses with a reverse transcriptase, they have not yet produced transformation in vitro or in vivo, in spite of extensive attempts to elicit transformation or tumor induction with these two agents.

To date, 20 months after inoculation, 10 percent brain suspensions and suspensions of the transformed SG cell line have not induced Creutzfeldt-Jakob disease in primates.

The virus particles present in our human brain cell cultures do not fit the morphological definitions of either type C or type B particles; they do resemble Mason-Pfizer monkey virus (MP-MV) described by Chopra and Mason (*2*). In collaborative studies, we have transmitted the SG virus to a human sarcoma cell line and demonstrated in these cells an RNA-dependent DNA polymerase that immunologically cross-reacts with the DNA polymerase of MP-MV (*3*). The SG transformed cell line itself does not contain reverse transcriptase activity. Also, the protein patterns of the SG virus and MP-MV, as analyzed by polyacrylamide gel electrophoresis, are similar in the number and relative size of peaks. The MP-MV cell line was in our laboratory when the SG cell line was established; it was not present for 35 days before transformation of the SG cell line was observed. Although the likelihood of cross-contamination is considered remote, the possibility lingers. However, attempts to induce transformation with MP-MV in human cell lines have been unsuccessful to date. Further studies are required to determine if the SG agent and the MP-MV are separate isolates of a similar virus. Additional isolations of these viruses will be necessary to resolve the question. At the present time, it would appear that the question of whether papovaviruses, paramyxoviruses, or viruses containing reverse transcriptase (such as MP-MV) are associated with human disease can best be answered with careful natural history studies.

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