suspending medium. Tissues were removed 1 hour after the last injection of the drug in order to determine enzyme activity. The mean results of three consecutive experiments are summarized in Table 1. It is evident that there is no significant difference in the activities of three enzymes taking part in glutamic acid metabolism in brain nor is there any significant difference in the activities of glutamic dehydrogenase and glutamic oxalacetic transaminase in liver. Lactic dehydrogenase, an enzyme requiring diphosphopyridine nucleotide but without any direct relation to glutamic acid metabolism, also was unaffected by thalidomide treatment in vivo. The injection schedule in these experiments may be considered adequate for producing the various derivatives of the drug in the body, and it may therefore be concluded that neither thalidomide nor its catabolic products cause a significant alteration in the activity of these enzymes in these two mouse tissues.

These results are not surprising since thalidomide has proved quite nontoxic in a variety of tests even at very high doses in various animal species, with the exception of its now well-known, highly specific, and selective teratogenic effect in man. Since it was shown recently (*8*) that congenital malformations can be produced by thalidomide in mice, an experiment was carried out to assess the effect of this drug on the enzyme content of the embryos of pregnant mice. A group of Paris mice were given three successive daily doses of thalidomide (250 mg/kg per day subcutaneously) on days 6, 7, and 8 after the presumed date of conception. Controls were given three injections of 30 percent propylene glycol, the solvent for the drug, on the same days. All mice were sacrificed about 20 hours after the last treatment; the mice which were found not to be pregnant were discarded. From the remaining mice (that is, 32 out of 95 in the thalidomide group and 10 out of 31 in the control group), the embryos, together with the contiguous portions of the uterus, were removed and extracted. The extracts were promptly assayed for glutamic dehydrogenase, glutamic oxalacetic transaminase, and lactic dehydrogenase by the procedures already outlined. No appreciable differences in enzyme activity, expressed on the basis of the total nitrogen of extracts A and B, were observed between the control and thalidomide groups.

These experiments were undertaken to test the working hypothesis—advanced by several groups of investigators—that this teratogen or its catabolic products may interfere with the biochemical or physiological functions of glutamic acid. Our results lend no support to this postulate.

Note added in proof: In independent studies on rat brain and rabbit fetuses, Fabro *et al.* reached the same conclusions (*9*).

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10. This work was supported by U.S. Public Health Service research grant CY 2332 C8 and Health Research Council of the City of New York grant I-109 (J.E.U.). We are indebted to the Wm. S. Merrell Co. for a supply of thalidomide.

18 November 1963

Experimental Reversal of Germ Cells in Ovaries of Fetal Mice

Abstract. *When heterosexual pairs of gonads of fetal mice were homotransplanted in close contact with each other below the kidney capsule of castrated adult hosts, the testis developed normally for this environment, but the ovary became an ovotestis. The medulla of the ovotestis contained dilated seminiferous tubules in which spermatogenesis progressed to the point at which secondary spermatocytes were produced. Under these conditions, germ cells, genetically determined as ova, underwent differentiation toward spermatozoa. This is the second clear case of germ cell reversal by experimental means in a mammalian species.*

Postgenetic sex reversals, under natural and experimental conditions, have been studied in a variety of vertebrates including teleosts (*1*), elasmobranchs (*2*), amphibians (*3*), reptiles (*4*), and birds (*5*). The conclusion emerging from investigations of this type is that the germ cells differentiate in response to internal environment rather than to their own genetic constitution. There are good reasons for believing that the region of the gonad in which the germ cells reside is a more potent factor in determining the direction of differentiation than are genic and chromosomal elements in the germ cells. The breeding of sex-reversed fishes, amphibians, and birds has provided unequivocal evidence that the genome is not impaired or otherwise changed by the procedures employed in producing the reversal.

While there are no reasons for believing that these principles do not apply to mammals, the mammalian gonads possess a remarkably stable organization and are difficult to modify or reverse. With few exceptions, attempts to alter the gonads have either yielded negative results or produced changes so minor in character as to be unconvincing. The masculinized ovaries of cattle freemartins are well known (*6*), and the condition has probably been duplicated experimentally by homotransplanting embryonic ovaries of the rat and mouse to the testes of adult hosts (*7*). The clearest and most complete instance of experimental gonad reversal in mammals, and the only one to be produced by the administration of exogenous steroids, has been obtained by Burns (*8*) in studies on young opossums (*Didelphis virginiana*). Burns found that when proper amounts of estradiol dipropionate were administered to pouch young in the ambisexual stage of development the testis became an ovotestis containing ovocytes in the cortical component. Jost (*9*), working with rabbits, attempted to transplant testes from 20-day fetuses contiguous to the intact ovaries of fetal recipients and, in a single instance, a testis and an ovary grew together for 8 days, causing the latter to become modified into a kind of ovotestis.

Macintyre (*10*) homotransplanted heterosexual pairs of fetal rat gonads beneath the kidney capsule of castrated adult hosts and, when the gonads were in close contact and of the same age, the testis differentiated normally, whereas the ovary generally formed tubular structures resembling testis tubules. The tublar elements of the modified ovaries contained ovocytes. The conclusion was reached that the capacity of contiguous heterosexual grafts to modify one another was due to the release of diffusible substances considered to be of the nature of corticomedullary in-

ductors. Comparable experiments in the rabbit were reported by Holyoke (*11*) and Beber (*12*). These considerations formed the basis of the experimental design of our studies on the mouse.

Charles River CD-1 mice were used for the most part, although several inbred strains were employed to make certain that immunologic reactions of the host were not playing a role in the kinds of differentiation we obtained in the grafts. Adult male hosts, castrated 1 to 6 months previous to transplantation, served as hosts; the donor gonads were obtained from 12½- to 14½-day fetuses. Seventy-six pairs of fetal testes and ovaries were transplanted contiguous to each other below the kidney capsule and allowed to persist for 21 to 60 days. Two milligrams of cortisone acetate, administered subcutaneously on alternate days, were found sufficient to prevent host rejection. All of the double grafts were recovered. Most of them were fixed in Bouin's fluid, but some were fixed in Zenker-formol and followed by the periodic-acid-Schiff technique to identify early spermatids in case they were present.

Forty-three of the grafts were removed after 21 to 35 days, and these presented a consistent histologic picture. The ovaries were ovotestes composed of both cortical and medullary elements, with the latter predominating. Ovocytes in early stages of follicle formation were apparent in areas of the cortex, whereas the medulla consisted of conspicuous, dilated tubules. There were a few ovocytes in the lumina of these tubules: some of these were degenerating, but others had one or several follicle cells appended to them and appeared normal. The tubules of the medulla were surrounded by a basement membrane, and early stages of spermatogenesis were observed within them. In addition to sustentacular cells of Sertoli, spermatogonia and primary spermatocytes (leptotene, zygotene, pachytene, and diplotene stages) were identifiable. Secondary spermatocytes were sparse, but some were found in several of the modified ovaries. No spermiogenic stages were observed in either ovarian or testicular portions of the composite grafts. It is apparent that spermatogenesis progressed as far in the ovotestis as it did in the contiguous testis persisting in the same transplantation site.

There was no possibility of confusing grafted testes and reversed ovaries since the tunica of the testis clearly delimited the two organs in most instances. Moreover, the ovary developed as an ovotestis when it was transplanted a short distance from one or more fetal testes, thus providing assurance that the components of the ovotestis did not arise from an intermingling of the two kinds of grafts.

The testicular parts of the grafts started to differentiate normally, but, on account of intraperitoneal temperatures, they were equivalent to cryptorchid testes and showed the same spermiogenic and hormonal impairments. After 40 days the testicular grafts appeared to lose supremacy and some of the ovarian grafts developed large follicles and showed other signs of recovery.

It is evident that the fetal testis is the source of a transmissible morphogenetic agent (or agents) which masculinizes the contiguous ovary. Many lines of evidence indicate that the fetal testis starts secreting androgens at an early age (*13*) and, while these may not be identical with the steroids of the adult testis, they have some of the same effects and appear not to be profoundly different. Whether the testicular material influencing gonadal differentiation is a steroid, a mixture of steroids, an unidentified hormone, or some kind of non-steroidal inductor substance must await further clarification.

So far as we are aware this is the first study on a mammalian species indicating that germ cells genetically determined as ova have been experimentally reversed and induced to differentiate in the male direction as far as secondary spermatocytes. Since spermiogenesis could not be expected in *kidney* grafts, exploratory studies are in progress to determine whether mature spermatozoa can be produced by reversed ovarian grafts residing in sites where temperatures are lower than in the peritoneal cavity. Incontrovertible evidence of ovarian reversal could be obtained if it eventually becomes possible to produce fully-formed germ cells suitable for use in breeding tests.

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14. The technical assistance of Hsien-sung Lin is acknowledged. Aided by research grants from NIH (HD-00597-02) and the Health Research and Services Foundation of Pittsburgh (F-22).

8 January 1964

Respiratory Distress: Relation to Prematurity and Other Factors in Newborn Monkeys

Abstract. *A respiratory distress syndrome resembling that seen in human infants was encountered in 4 out of 90 rhesus monkey infants after uncomplicated births. These were nonviable immature infants weighing less than 350 grams. A much higher incidence of respiratory distress was observed in those whose births were complicated by experimental procedures, mainly asphyxiation. Thirty-four out of 68 infants developed the syndrome, the incidence being greatest among the least mature.*

A condition resembling the human respiratory distress syndrome was observed in lambs and monkeys asphyxiated during cesarian-section delivery (*1, 2*). I have examined the roles of prematurity and other factors in its occurrence in monkeys (*Macaca mulatta*).

Respiratory distress in the monkey is defined as a condition appearing soon after birth and persisting for more than an hour, in which the lower end of the sternum and costal margins of the newborn are drawn in during inspiration as the respiratory efforts become increasingly forceful, and the expirations