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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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

Table 1. Incidence of the respiratory distress syndrome (RDS) in the control group of monkeys and in the experimental group in which complications at birth were artificially induced. Number born by cesarian section in parentheses.

Weight at birth (g)	Number born	No. with RDS	Deaths by day 2
Control group: uncomplicated deliveries			
> 500	24 (5)	0	0
400–400	47*(15)	0	0
< 400	19 (7)	4†	4
Experimental group: complicated deliveries			
> 500	22 (21)	9	1
400–499	28 (28)	14	4
< 400	18 (16)	11	9

* One of these was immature, born vaginally at 136 days, but weighed 440 g. † Two vaginal and two cesarian births.

sometimes produce "grunting" sounds. The newborn monkey is pale, the respiratory rate is rapid (110 to 160 per minute) and, even when it is provided with oxygen in high concentrations, cyanotic attacks with gasping or periods of interrupted or irregular breathing occur. Transient signs of distress, such as chest retraction or cyanotic episodes, may be encountered occasionally during the first hour after delivery of immature monkeys of light weight, but such symptoms are of brief duration and do not recur. Pulmonary edema is frequently associated with persistent distress, and if morbidity is prolonged and death comes slowly, amorphous material may be found in the lung alveoli at necropsy.

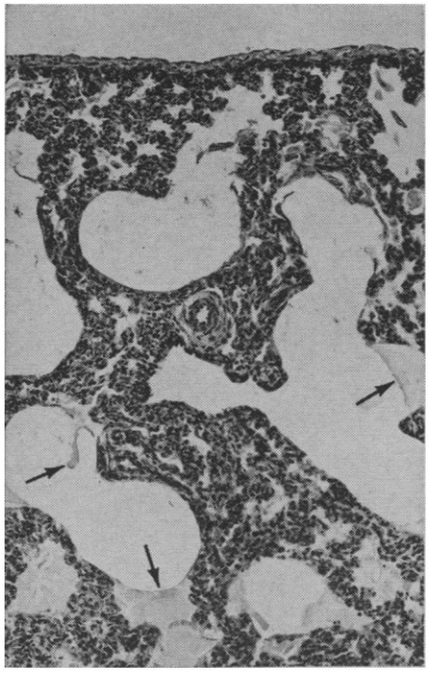

Fig. 1. Atelectatic lung of a naturally delivered premature monkey infant that developed the respiratory distress syndrome, became morbid, and died on the second day. Amorphous material was present on the walls of the few dilated alveoli (arrows). (Haematoxylin and eosin; × 200)

A control group of 90 monkeys born vaginally or by uncomplicated cesarian-section delivery under local anesthesia were examined at birth to determine the incidence of the respiratory distress syndrome in relation to birth weight. The monkeys were born in a caged colony; spontaneous deliveries took place in the squatting position, after labor lasting an hour or more in some cases. Cesarian sections were performed on animals restrained in the supine position with tissues of the abdominal wall infiltrated with procain hydrochloride; no other drugs were used. Table 1 shows the distribution of the syndrome in this control group. The four monkeys that developed the syndrome weighed 241, 246, 305, and 322 grams. In four others that weighed less than 350 grams the syndrome did not appear.

The incidence of the respiratory distress syndrome was much greater among animals treated experimentally. Various procedures were used with 68 other monkeys before, during, or after delivery which was mainly from the supine position by cesarian section under local anesthesia. The procedures for 25 monkeys were as follows. Oxytocin was administered to six adults to elevate intrauterine pressure; all six offspring developed the syndrome (*3*). Solutions of bilirubin were given to seven newborn animals that had been asphyxiated for 9 to 12 minutes; six of these animals developed the syndrome (*4*). Twelve newborn monkeys received exchange transfusions, or injections of cellular carcinogenic material, or both; one monkey that received an exchange transfusion developed the syndrome (*5*). The results obtained with these monkeys are combined in Table 1 with the results for 43 others which had been asphyxiated for 10 to 15 minutes at birth and resuscitated by procedures described previously (*6*). The results for the 43 monkeys are described by Adamsons *et al.* (*1*).

The fact that spontaneous respiratory distress syndrome was limited to previable immature offspring of monkeys suggests that the lungs may not have attained a state of development that permitted expansion. Histological examination of lungs of monkeys dying after they had developed the syndrome revealed extensive atelectasis of the type characteristic of fetal lungs, with only a few widely dilated alveoli. The linings of the alveoli were coated with an amorphous material (Fig. 1). Even at full term, the lungs of guinea pig fetuses resembled glands and appeared to function as such until required for respiration (*7*). The lungs of mature fetuses expand readily at the time breathing begins, but those of immature fetuses cannot expand sufficiently to prevent anoxemia from ensuing. The margin of safety increases with the age of the fetus and its structural maturity. The respiratory distress syndrome reflects the reaction of the individual to anoxemia.

Interference with the normal course of events at birth and imposition of unnatural burdens on the monkey infants induced the development of the distress syndrome in 50 percent of the experimental group. The phenomenon appeared and deaths during the first 48 hours occurred most frequently in the smaller offspring. All the animals represented in the experimental group (Table 1) were more mature than the four controls which died after developing the syndrome. Thus, prematurity cannot be considered to be the sole cause of this condition.

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