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Received February 14, 1952. P.S.E.B.M., 1952, v79.

Pancreatic Disease in Mothers of Suckling Mice Infected with Connecticut No. 5 Strain of Coxsackie Virus.* (19420)

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It has been the practice in this laboratory, when infecting suckling mice with one or another strain of Coxsackie virus, to discard the mother at the completion of the experiment. But when it was shown that adult mice are susceptible to infection with the Connecticut No. 5 strain(1), it was decided to keep some of the mothers under observation in order to determine whether or not they might become spontaneously infected.

Thus, the mothers of 19 litters were examined microscopically at various intervals after infection of their young with Conn.-5 virus. Seven of these showed histologic evidence of pancreatic disease, which appears to be the principal pathologic effect of infection of adult mice with the Conn.-5 strain. Microscopic examination of the pancreas and liver of mothers naturally infected through their offspring reveals the same pathologic lesions which are characteristic of pancreatic disease produced experimentally in adult mice(1). Fig. 1 is a photomicrograph of a section of pancreas of a mother mouse which was found dead 9 days after inoculation of her young and 6 days after she had ingested 2 of them. There is a massive early necrosis of the entire pancreas. There was also severe hepatitis, with hyaline necrosis of many liver cells, and fatty infiltration of others, and many phospholipid containing cells in the sinusoids. In general, the character of the pancreatic lesions coincided fairly well with the period elapsing between the presumed ingestion of the infected young and the day of death or sacrifice. Thus there was massive necrosis in those mice surviving only 6 days, whereas those which lived 10 to 12 days presented subacute lesions (Fig. 2). At this time the necrotic acinar cells have been removed and the remaining pancreas consists almost entirely of islands and ducts embedded in loose areolar or fatty tissue thickly infiltrated with histiocytes. Hepatitis of varying degrees of severity was found in some animals. Fig. 3 shows extreme fatty infiltration of the liver, with necrosis of individual liver cells.

The more obvious methods by which the mothers might acquire this viral infection from their offspring are: 1) by ingestion of the excreta of the sucklings, 2) by eating the sick or dead mice in their litters, and 3) by inhalation of infectious materials. In addition to the infected baby mouse carcass, both urine

* Aided by a grant from the National Foundation for Infantile Paralysis.

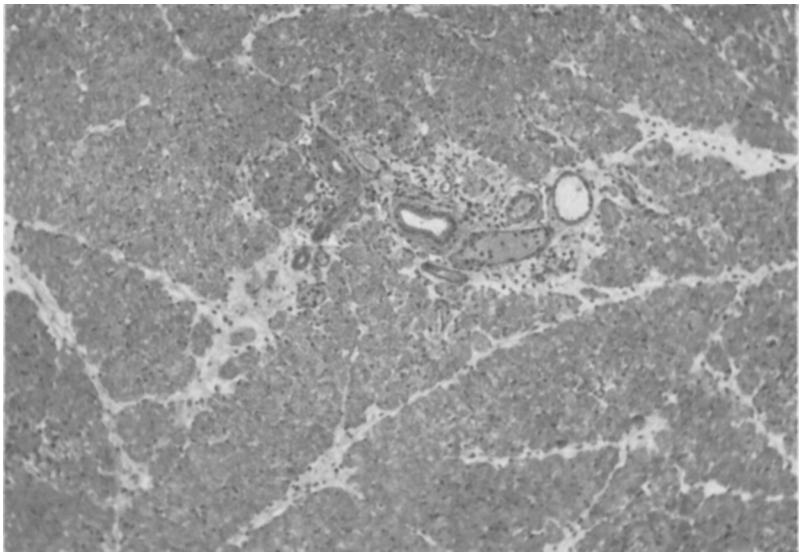

FIG. 1. Mouse 4600. Mother died 9 days after inoculation of offspring with 10^{-3} Conn.-5 virus, 6 days after ingestion of 2 dead young. Massive necrosis of entire pancreas. Island of Langerhans and ducts have escaped destruction. HE × 100.

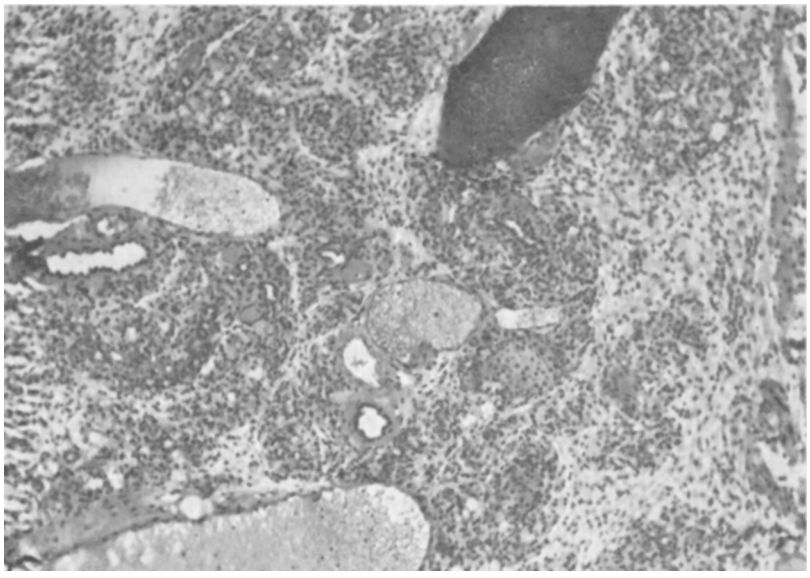

FIG. 2. Mouse 4637. Mouse sacrificed 16 days after inoculation of offspring with 10^{-4} suspension of Conn.-5 virus. Pancreas: Complete loss of exocrine tissue; interstitial histiocytic reaction; preservation of islands and ducts. HE × 83.

(2) and feces(3) contain active virus.

In order to determine the manner in which the mothers most probably become infected, the following experiment was performed: Ten litters (6 to 9 mice per litter) of 0- to 1-day-old mice were inoculated intraperitoneally with approximately 1000 LD_{50} of Conn.-5 virus. The litters, with their mothers, were kept in individual cages for 72 hours. Close attention was paid to the number of sucklings which disappeared during this time—presumably eaten by the mothers. On the 4th day all of the mice were removed from the original cages and redistributed in the following man-

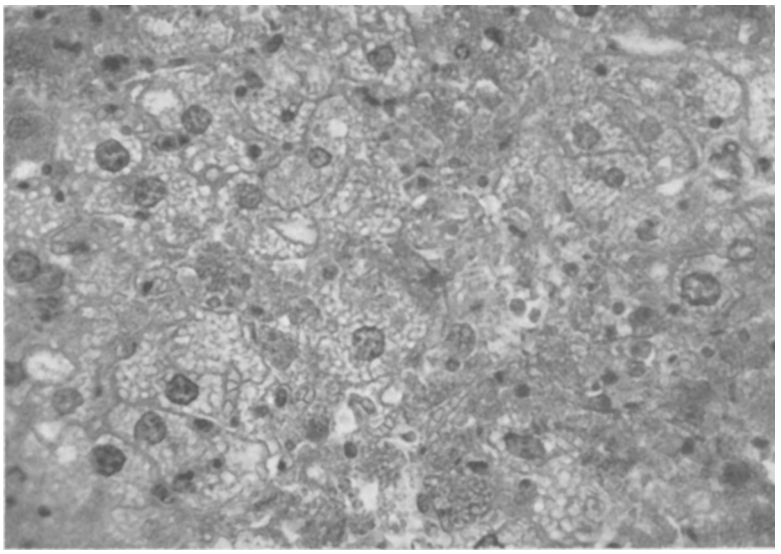

FIG. 3. Mouse 4599. Mother died 17 days after inoculation of offspring with 10^{-2} Conn.-5 virus, 10-12 days after ingesting 2 dead young. Liver: Extreme fat infiltration; necrosis of scattered parenchymal cells. HE × 400.

ner. Each mother was placed in a new individual cage for further observation. Normal 7-week-old mice were exposed to the infected material of the original cages by being quartered in them, one to a cage, until the termination of the experiment. The carcasses of the infected suckling mice were fed to an additional group of normal adults. Ten 7-week-old mice in individual cages were each given 3 sucklings which they rapidly consumed. All of the mice were observed for an additional 15 days, after which they were sacrificed for histologic examination. The results, presented in Table I, indicate that adult mice are probably infected neither by ingesting excreta of their young in the first 3 days after inoculation nor by the cage litter which has been contaminated by the infected suckling mice. Rather, it would appear that adult mice can and do develop pancreatic disease after ingesting the carcasses of infant mice infected with Conn.-5 virus.

TABLE I. Experimental Pancreatic Disease in Adult Mice.

Exp. conditions	No. mice	Sex	Pancreatic disease	
			Present	Absent
1. Mothers of infected litters*	10	♀	0	10
2. Quartered in	8	♀	0	8
dirty cages	2	♂	0	2
3. Consumed infected carcasses	5	♀	3	2
	5	♂	4	1

* Four of the mothers ate one or 2 carcasses during the first 3 days.

In other experiments it was impossible to produce pancreatic disease in adult mice by feeding 10000 LD_{50} of Conn.-5 virus in a dough of whole wheat flour and skim milk; in another experiment one out of 6 adult mice developed pancreatic disease after ingestion of a single carcass of an infected suckling mouse. Moreover, a single attempt to infect adult mice by the intranasal instillation of Conn.-5 virus was unsuccessful as judged by the failure to find signs of pancreatic disease in the inoculated animals.

Evidence that the pancreas of naturally infected mothers contained virus was obtained by inoculating into 0-day-old mice, 10^{-2} and 10^{-4} dilutions of a pool of pancreas tissue suspension obtained from 3 mothers. All of the inoculated mice succumbed and 2 of them, which were examined histologically, showed the usual pancreatitis and hepatitis.

Discussion. There have been few previous studies bearing on the possibility of infection with Coxsackie viruses by oral administration. Melnick and associates (4,5) have found that

chimpanzees and cynomologous monkeys, though showing no apparent illness which could be ascribed to the virus, readily became carriers and developed neutralizing antibodies. Kaplan and Melnick(6) have also shown that newborn mice are susceptible to oral infection with 5 different strains (4 immunologic types) of C virus, though not all of the mice became infected. Adult lactating females could not be infected with the High Point strain by feeding. The authors say that they have "observed many adult female mice who cannibalized their infected young without effect on the mothers." Whether this included mothers of sucklings infected with the Conn.-5 strain is not stated.

Since it has been shown that the mothers may become spontaneously infected with the Conn.-5 strain of Coxsackie virus and since those that survive may develop neutralizing antibodies which, by placental transmission or through lactation might protect their offspring, it is obvious that subsequent litters would be unsuitable for experiments with this strain. That this might also apply to other strains of Coxsackie virus is suggested by the recent finding that the Powers(7) and DeMole(8) strains are also capable of producing pancreatitis in adult mice(9).

Summary. Mothers of suckling mice may spontaneously become infected with Conn.-5 strain of Coxsackie virus, following inoculation and infection of their young with this virus. They develop pancreatic lesions and, in some cases, hepatic lesions identical with those produced after intraperitoneal injection of virus. This condition can be reproduced experimentally in adult mice of either sex by feeding them with the carcasses of infected suckling mice.

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Received February 14, 1952. P.S.E.B.M., 1952, v79.

Influence of Glomerular Filtration Rate upon the Renal Tubular Reabsorption of Sodium.*† (19421)

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In a recent study(1), the administration of hypertonic saline to dogs resulted in an increased rate of sodium reabsorption in every case. Since the rise in plasma sodium concentration was accompanied by a variable, but consistently present, elevation of glomerular filtration rate in each experiment, it was not possible to determine the factor which was responsible for the altered rate of sodium reabsorption. Other investigators also have observed changes in glomerular filtration rate subsequent to hypertonic saline infusions, the usual effect being an augmentation(2-3), although reduced filtration rates have occurred in some cases(4).

In the present series of experiments the administration of hypertonic saline exerted only a negligible effect upon the rate of glomerular filtration in six out of eight experi-

* This paper was presented in abridged form at meeting of the American Physiological Society, April, 1951.

† Supported by a grant from the U. S. Public Health Service.

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