of foods. One will also expect to find an occasional case of food poisoning when, by chance, a rare concatenation of events will result in significant production of toxin in foods by bacterial species not ordinarily considered food poisoning organisms (*5*).

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Effect of 5-Hydroxytryptamine and Iproniazid on Pregnancy

Abstract. The effects of 5-hydroxytryptamine and iproniazid on pregnancy in mice and rabbits were investigated. 5-Hydroxytryptamine can interrupt pregnancy at all stages in mice but is particularly effective early and late in pregnancy. Iproniazid exerts its action essentially in the first half of pregnancy. 5-Hydroxytryptamine produces striking hemorrhage in the placenta.

We were led to investigate the effects of 5-hydroxytryptamine (5-HT) and iproniazid on pregnancy, in view of the facts that (i) 5-HT is liberated in the body by reserpine (*1*), which has an effect on pregnancy in rats (*2*) and (ii) iproniazid inhibits the destruction of 5-HT by monoamine oxidase and is known to increase the level of 5-HT in rats (*3*).

Experiments were carried out on female mice of known fertility. The first day of pregnancy was counted from the finding of the vaginal plug. The animals were treated subcutaneously at various stages of pregnancy, since it had been shown previously that different drugs are effective at different stages (*4*). 5-Hydroxytryptamine was given in two divided doses per day, while iproniazid was given in a single daily dose. Treatment was given in the following periods: 1 to 6 days, covering the preimplantation zygotic development; 3 to 8 days, covering the period of implantation; 6 to 11 days, covering the early stages of decidua formation; and 11 to 16 days, covering the stage of well-developed placenta and well-differentiated fetus. The animals were observed for signs of vaginal bleeding and loss of weight. Laparotomy was performed on the day after the end of treatment. The results are shown in Table 1.

It is obvious that both drugs have effects on pregnancy though not exactly at the same stage. The effects of 5-HT appear to be most striking in the early and late stages of pregnancy, while iproniazid has marked effects in the first half of pregnancy, particularly at the period covering implantation, and little effect later on. The results suggest that one of the effects of both of these drugs is to prevent implantation.

The marked effects of 5-HT on established pregnancy led to a more detailed investigation at this stage, all experiments being performed on the 14th or 15th day. Animals were injected with total doses of 4, 2, 1, 0.375 to 0.5, and 0.15 to 0.24 mg of 5-HT given in divided injections spread over a period

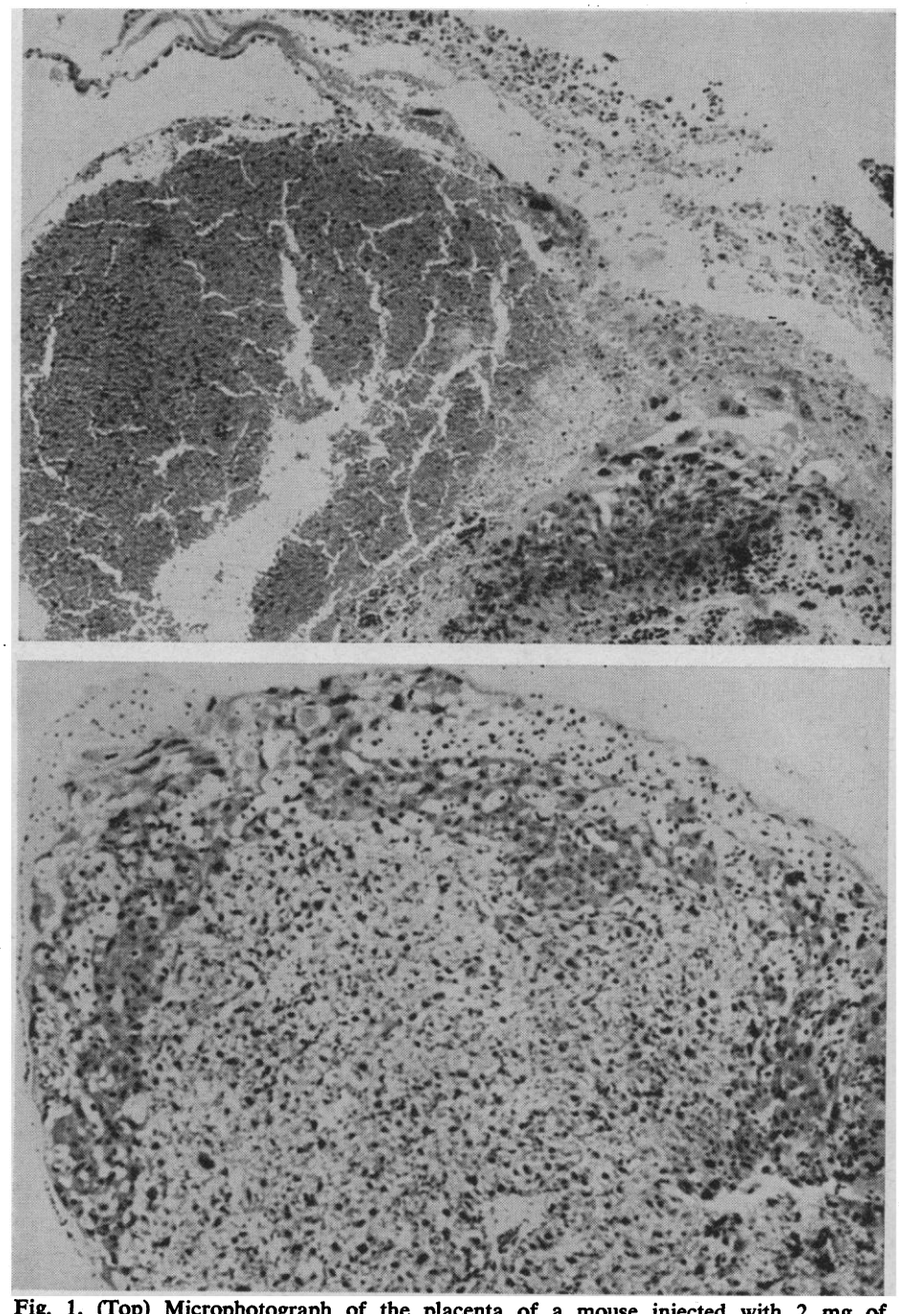

Fig. 1. (Top) Microphotograph of the placenta of a mouse injected with 2 mg of 5-HT (seven injections) on the 14th day of pregnancy and killed the next day. (Bottom) Normal placenta at the same stage of pregnancy. (About × 72.5)

of 1 day, or of 3 to 4 days in the case of the last two doses. Interruption of pregnancy was complete (2/2 and 9/9) in animals treated with doses of 4 and 2 mg, respectively, but was incomplete (1/4, 3/7, and 2/8, respectively) in the remainder. Intravenous injection of 0.25 mg of 5-HT in three mice at the same stage of pregnancy had no effect.

Thus it is obvious that 5-HT, even in small doses, can interrupt pregnancy. In such cases the uterus appeared dark, and in some cases almost black, in color at laparotomy. When the uterus was opened, the placentas showed gross hemorrhagic changes, mostly involving the fetal part, while the amniotic sac contained the reabsorbing fetus in the form of a yellow gelatinous material. In some of the animals that had received the smaller doses of 5-HT and in which pregnancy appeared normal, minute hemorrhages in the placentas were nevertheless obvious to the naked eye. Histological examination of the placentas of animals in which pregnancy had been disturbed revealed massive collections of red blood corpuscles just under the surface and disorganization of the normal villous pattern (see Fig. 1).

In an attempt to determine how rapidly 5-HT could produce deleterious changes in the uterine contents, nine mice in an advanced stage of pregnancy (17 days) were injected subcutaneously with a single dose of 1 or 2 mg of 5-HT and examined at intervals ranging from ½ to 3½ hours after the injection. In two animals injected, respectively, with 2 and 1 mg of 5-HT and examined ½ hour later, there were obvious hemorrhagic changes in all the placentas, and all the fetuses were already dead. Some of the fetuses in animals examined later were still alive, but the placentas of these animals showed hemorrhagic changes, and the placentas of all animals killed 2 or more hours after the administration of 5-HT showed marked hemorrhagic changes. It is obvious, therefore, that 5-HT can very rapidly produce hemorrhage and disorganization of the placenta, leading to death of the fetus.

Table 1. Effect of 5-HT and iproniazid at various stages of pregnancy in mice. The ratios represent the number of animals found pregnant out of the total number of animals used.

Period of treatment (day No.)	5-HT (1 mg/day)		Iproniazid (5 to 10 mg/day)	
	Control	Treated	Control	Treated
1–6	19/27	4/27	13/26	5/24
3–8	7/12	1/12	12/14	2/14
6–11	15/26	8/26	12/20	0/15
11–16		0/11*	9/13	9/13†

* All animals were pregnant on the 11th day —that is, before treatment was started.
† Three litters were born dead at full term.

Experiments on rabbits gave rather similar results, including hemorrhage in the placenta. The most marked effects were seen late in pregnancy.

The fact that relatively small doses of 5-HT can interrupt pregnancy and produce in the placenta hemorrhages which simulate findings in the human placenta in the toxemia of pregnancy [where red infarcts are constantly observed (*5*)] raises the question whether 5-HT is involved in the pathogenesis of toxemia (*6*).

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Viruses Associated with Epidemic Hemorrhagic Fevers of the Philippines and Thailand

Abstract. Epidemiologic, clinical, and etiologic studies were carried out on a newly recognized, frequently fatal, pediatric disease syndrome which occurred in urban areas infested with *Aedes aegypti* mosquitoes. Four types of dengue virus (two of which are new), chikungunya virus, and another virus yet to be identified were isolated from the blood of patients. Dengue viruses, types 2 and 3, were isolated from the mosquitoes. Ample serologic confirmation was obtained of concurrent hemorrhagic fever and infection with one or more of these viruses. Thus, it was discovered that viruses of previously recognized types and of closely related new types apparently have etiologic roles in a new and highly dangerous epidemic disease syndrome.

Pediatricians observed a number of cases of a serious, frequently fatal, hemorrhagic, febrile disease in Manila, Luzon, in the rainy season of 1954. It was described as a new disease entity and named Philippine hemorrhagic fever (*1*). During the rainy season of 1956, a large epidemic occurred in Manila. This coincided with a search for the arthropod-borne [ar-bo (*2*)] viruses of the area that was being made by a field research unit (*3*) under the direction of one of us (W.M.H.) Observations of a clinical, epidemiologic and laboratory nature on hemorrhagic ("H") fever were included in the study, though no relation to arthropod transmission was then recognized.

Over 750 cases of "H" fever were reported in Manila during the rainy-season months of July through October; approximately 10 percent of the cases were fatal. With few exceptions the disease occurred in children, predominantly below 6 years of age; all were orientals, in urban or suburban areas where *Aedes aegypti* were present in relatively large numbers. Cases were not found where *A. albopictus* but not *A. aegypti* were present. The disease, although having some similarities to the epidemic hemorrhagic fever of Korea and Manchuria, could be readily differentiated clinically; also, it did not closely resemble yellow fever, leptospirosis, or Omsk or Crimean hemorrhagic fevers.

As a result of a preliminary report (*4*) on the disease, one of us was requested to study an alarming epidemic which occurred in and near Bangkok during the rainy season of 1958. Here again a distinctive hemorrhagic disease had been first recognized in 1954, occurring as a small epidemic among children, and a few cases had been observed annually thereafter at the same season. Approximately 2500 hospitalized cases and 250 deaths marked the major epidemic observed and reported here. Clinically the disease resembled rather closely that observed in Manila, but it differed in significant ways; this led the clinical observer of cases in both areas (W.M.H.) to expect to find a related but different etiologic agent. The age and race of the patients and the seasonal and urban distribution of the diseases in Thailand and the Philippines, were similar, as well as the marked association with *A. aegypti.*

Mosquitoes from the area and blood sera from patients in the acute and convalescent phases of the disease were collected, frozen in dry ice, and transported to Pittsburgh. Sera, in several dilutions, from patients in the acute phase and mosquito suspensions by species were inoculated intracerebrally into suckling mice and passaged blindly when necessary. Because of the possibility suggested by epidemiologic findings that dengue-related viruses might be involved, the surviving mice were challenged with dengue virus type 2,