highly instructive cave hinges on the behavior of the water table that controls the depth to which one may penetrate.

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Pyretogenic Effect of Lysergic Acid Diethylamide

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Whereas most of the ergot alkaloids exhibit oxytocic or peripheral autonomic effects, lysergic acid diethylamide (LSD) shows little or none of these actions but rather a hallucinogenic effect (*1, 2*). In studying the effects of LSD in intact normal rabbits marked hyperpnea was noted. This led to a consideration of the possibility of the existence of increased body temperature, which was indeed found to be the case (*3*).

Most experiments were carried out on unanesthetized and otherwise untreated animals. The agent was supplied in ampuls containing 0.1 mg/ml and was administered either subcutaneously or intravenously without dilution. No significant difference was observed in the amount of the fever, but the time of onset and duration of action were somewhat shortened with the intravenous route of administration. A rise

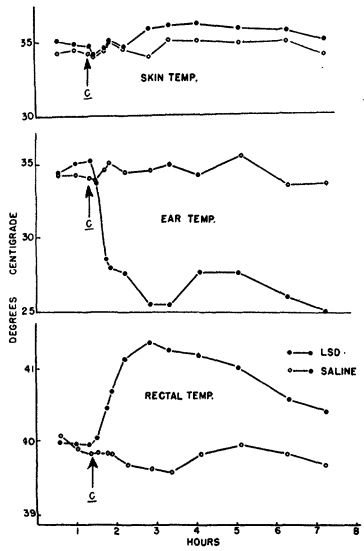

Fig. 1. Skin, ear, and rectal temperatures of a rabbit receiving 50 μg/kg of LSD subcutaneously and a control rabbit receiving an equivalent volume of saline.

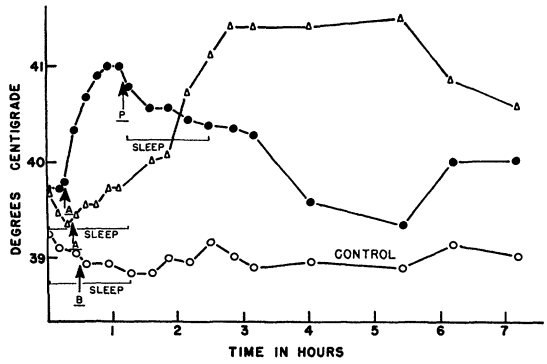

Fig. 2. Effect of the administration of anesthetic doses of sodium pentobarbital of 30 mg/kg intravenously on the pyretogenic effect of 50 μg/kg LSD administered intravenously. In the curve indicated by triangles the pentobarbital was given at the height of the LSD effect. The lower curve is the rectal temperature of a control rabbit receiving pentobarbital only. Sleep indicates the period during which righting reflex was absent.

in rectal temperature was produced in rabbits, dogs, and cats, but the rabbit was most markedly affected and, hence, was used for certain subsequent experiments. Subcutaneous injections of 50 μg/kg of LSD in the rabbit produced a rise in rectal temperature within 10 to 20 min. The peak effect was reached after 2 to 4 hr. The total duration of the pyretogenic action was 7 to 9 hr.

Preliminary experiments were carried out in an attempt to clarify the mechanism of the pyretogenic action. In addition to rectal temperature, surface temperature of the skin and the ear was measured by a McKesson's model 205 Dermalor in several rabbits. The skin temperature was measured from a shaved area approximately 4 in.^{2} on the back of the rabbit. Figure 1 is a typical response from such as experiment. Skin temperature did not change significantly from that of a control rabbit, but the ear temperature fell markedly. This latter effect persisted throughout and far beyond the pyretogenic effect. This led to a consideration of the possibility that the rise in rectal temperature might be due to a vasoconstriction of the rabbit ear preventing radiation and raising the internal temperature. To test the role of the rabbit ears in the control of body temperature, the ears of a normal rabbit were clamped with hemostats. There was no change in rectal temperature during a period of 6 hr. Hence it is not likely that the pyretogenic effect of LSD is the result of this vascular effect.

Attempts were made to lower the LSD-produced fever by the administration of antipyrine, dihydroergotamine. Hydergine, and dibenamine. These were without effect. Sodium pentobarbital administered intravenously in doses of 30 mg/kg did affect the LSD-induced fever. Figure 2 shows this marked antagonism. Previous administration of this dose of sodium pentobarbital prevented the pyretogenic response of LSD for as long as the animal was anesthetized. Administration of this dose of pentobarbital at the height

of the temperature rise reduced the fever and restored the temperature to approximately normal.

Reports of the action of LSD in intact animals and human beings have been conflicting and undependable. Forrer and Goldner (*2*) report that two of five patients showed a slight rise in oral temperature after LSD. Reports of other actions of LSD on the cardiovascular system (*2*), central nervous system (*4*), and autonomic system (*5*) are likewise variable and equivocal. The pyretogenic effects reported here are reproducible and dependable, and so there is a possibility of taking advantage of this effect as an end-point in the investigation of the pharmacology of LSD. On the one hand, this effect may be part of the predominant central action. On the other hand, it may be simply a side action of this agent unconnected with its predominant central nervous system effects. Studies are being continued to determine the mechanism of this pyretogenic effect of LSD and to explore its usefulness in general pharmacologic studies of this agent.

Conclusions. Lysergic acid diethylamide produces a rise in body temperature of normal rabbits, cats, and dogs. This rise in temperature is antagonized by the administration of sodium pentobarbital but not by antipyrine or adrenergic blocking agents.

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Studies on *Pasteurella pestis* in Fleas: II. Experimental Blocking of *Xenopsylla cheopis* with an Avirulent Strain of *P. pestis*

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The classical findings (*1*) that fleas blocked with a proventricular mass of *Pasteurella pestis* were particularly significant plague vectors have been confirmed by numerous investigators (*2*). Nevertheless, to account for certain epidemiologic phenomena, some workers have suggested, without direct evidence, that the bacteria may undergo a loss of virulence in the flea (*3*). On the other hand, it is generally assumed that virulence of the plague bacillus cannot be increased in the flea. Nothing appears to be known about the fate of a completely avirulent strain of *P. pestis* in the flea. It is this problem that forms the basis for the preliminary observations reported here.

The development of an apparatus for the artificial feeding of fleas (*4*) made it possible to exert a high degree of control upon the number of bacteria ingested by the flea and to provide an efficient *modus operandi* for infecting fleas with avirulent plague strains. Thus by means of *in vitro* feeding of fleas, the oriental rat flea, *Xenopsylla cheopis,* could be given blood meals containing *P. pestis*. The data presented in Table 1 show the quantitative transfer of avirulent *P. pestis* strain A1122 (*5*) from the heparinized blood meal in the feeding apparatus to the flea. After infection, the fleas were maintained on white rats and removed when desired.

As was demonstrated by bacteriologic cultures, the plague bacilli multiplied rapidly after the first day in the ventriculus of the flea (Fig. 1). In the five female fleas that were macerated and plated out 2 days after infection, the bacteria count ranged from 1.1 to 6.0 million viable plague bacilli and averaged 3.0 million. In the five male fleas the range was from less than 5000 to more than 350,000, the average, 2.2×10^5 and the median, 2.6×10^5. The medians observed on any particular day did not represent as much as a twofold difference from either the averages or the actual bacterial counts of those fleas immediately above and below the median value.

The Indian Plague Commission (*6*) estimated the average stomach capacity of the rat flea, *X. cheopis,* to be 0.5 mm³. In the present study, the determinations made both by weighing the fleas and by counting the bacteria in them immediately after feeding show that the male has a greater body density but a smaller stomach capacity than the female *X. cheopis* (Table 1).

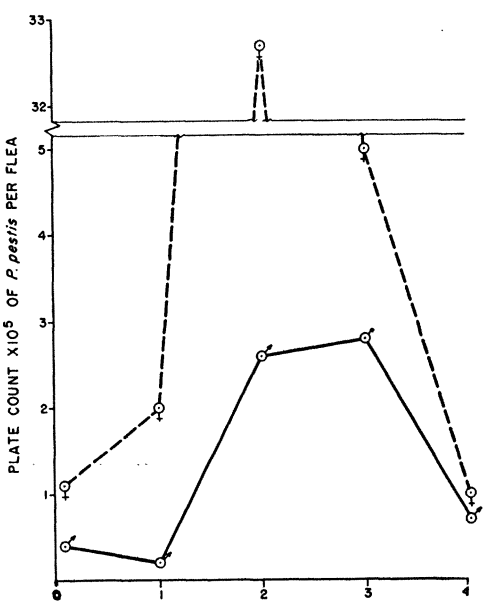

Fig. 1. The median *P. pestis* count in infected *X. cheopis* during the first 4 days after the infectious meal (each point represents the median of five fleas per sex).