Mechanisms that may be responsible for this relationship, and their bearing on certain problems of *in vivo* penicillin resistance, have been discussed.

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1. Maaløe, O., *Acta Path. Microbiol. Scand.*, 1948, v25, 414.

2. Treffers, H. P., Muschel, L. H., *J. Exp. Med.*, 1954, v99, 155.

3. Rowley, D., *Brit. J. Exp. Path.*, 1956, v37, 223.

4. Wardlaw, A. C., Pillemer, L., *J. Exp. Med.*, 1956, v103, 553.

5. Wedgwood, R. J., Pillemer, L., *Ann. N. Y. Acad. Sci.*, 1956, v66, 247.

6. Braun, W., *Bacterial Genetics*, W. B. Saunders Co., Philadelphia, 1953.

7. Lederberg, J., *Proc. Natl. Acad. Sci. U. S.*, 1956, v42, 574.

8. Park, J. T., Strominger, J. L., *Science*, 1956, v125, 99.

9. Szybalski, W., *Antibiotics and Chemotherapy*, 1953, v3, 915.

10. Litchfield, J., *J. Pharm. and Exp. Therap.*, 1949, v96, 399.

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Distribution of Terminal Temperatures in Hypothermic Dogs. (23659)

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Anesthetized dogs subjected to acute progressive hypothermia succumb in one of 3 ways(1). Under pentobarbital anesthesia the majority (60%) terminate in ventricular fibrillation (VF) at heart temperatures of 25°-19°C, terminus usually being preceded by extrasystolic activity. A proportion (15%) terminate in asystole at 18°-15°C. The remainder (25%) exhibit a period of asystole of variable duration (5-80 sec.) or an exceedingly slow heart rate (less than 16 b.p.m.) either of which is followed by VF. The latter type of death has been termed "asystolic fibrillation" (AF) and occurs at temperature range intermediate between the 2 former groups, *i.e.* 20-17°C(1).

It would be of interest to discover whether each group represented a distinct segment of the population or whether each type of death was a direct consequence of the terminal temperatures which were otherwise distributed along a predictable curve. Statistically the question is whether the population of animals employed was homogeneous regarding susceptibility to VF, *i.e.* whether terminal temperatures are uniformly distributed as opposed to a distribution exhibiting bi- or trimodalities. This could be determined only after a large group of "control" experiments had accumulated. Such a series of animals, similarly treated, is now available to make the analysis possible.

Methods. Results from a total of 110 mongrel dogs of both sexes, weighing between 8-18 kg, are included. All animals were anesthetized with pentobarbital (30-35 mg/kg) and cooled to terminus by immersion in an iced bath. Details of the method have been previously reported(2). Heart temperatures were measured thermoelectrically with a catheter thermocouple inserted into the right auricle via the right jugular vein. Rectal temperatures were measured with a rectal thermocouple. The accuracy of the temperature recording instrument is within $\pm$ 0.5°C. All animals were allowed to breathe spontaneously until a heart temperature of 25 $\pm$ 1°C was reached. At lower temperatures, they were respired artificially by means of a positive pressure respirator.

Results. When all terminal heart temperatures were plotted in a frequency nomogram, it became apparent that they deviated greatly from a Gaussian distribution. Nevertheless there was no evidence of bimodality to suggest that the animals terminating in asystole or asystolic fibrillation were derived from a different population from that showing extrasystoles followed by VF.

A simple transformation of the terminal

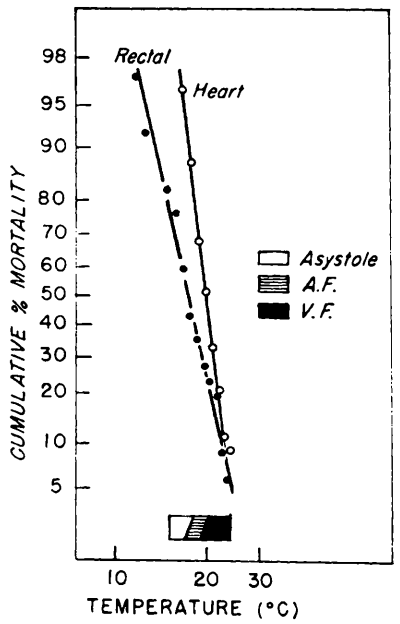

FIG. 1. Log-normal distribution of terminal temperatures in hypothermic dogs.

temperatures into their logarithmic equivalents revealed that this distribution, like many other biological variables, was in fact a log-normal distribution(3); *i.e.* the logarithms of the terminal temperatures were distributed along a normal Gaussian curve. Thus a probit-log temperature plot according to the method suggested by Gaddum(3) gives a good approximation of a straight line (Fig. 1) which is verified by a chi-square test using the method of maximum likelihood(4).

Similar results were obtained from the analysis of the rectal temperatures although the slope of the line and the median are different. This would be expected since it is known that in moderate hypothermia rectal temperatures are usually lower than heart temperatures and the 2 measurements show no strict parallelism during further cooling (2).

The median lethal temperature (LT_{50}) was found to be 20.1°C for heart temperatures and 19.8°C for rectal temperatures. The 95% confidence limits respectively were: 21.3 to 18.9 and 23.8 to 17.8.

Discussion. The analysis indicates that under the experimental conditions employed, the terminal temperatures of hypothermic dogs are distributed uniformly along a log-normal distribution curve with no evidence that the population of dogs was heterogeneous regarding susceptibility to hypothermia. It appears rather that dogs terminating in asystole or AF do not belong to a different segment of the population from those succumbing to VF. It seems most probable, therefore, that terminal events are related to terminal temperatures rather than vice versa. This is of particular importance, since it places major emphasis on terminal temperature rather than mode of death.

However, this conclusion may not be valid in the case of animals subjected to modifications of the standard procedure, *e.g.* administration of pharmacologic agents, since such agents may depress the myocardium and precipitate asystole at relatively high temperatures, or conversely predispose to fibrillation at temperatures above or below the range of controls. Nevertheless, the analysis here presented provides a potent tool for the investigation of pharmacologic or other agents on the responses of the hypothermic heart. Probit-log temperature curves can be plotted for treated and control groups and a statistical comparison made which would include not only the median temperature and its confidence limits but also the slope of the probit line, *i.e.* the spread of the mortality distribution.

Summary. The distribution of terminal temperatures following induced hypothermia in dogs was statistically analyzed for evidence of inhomogeneity. It was found that the data from over 100 animals could be adequately expressed by a log-normal distribution without any evidence of heterogeneity. This suggests that the different terminal events (*i.e.* fibrillation *vs.* asystole) which occur under induced hypothermia are determined by the terminal temperatures rather than vice versa.

1. Covino, B. G., Charleson, D. A., D'Amato, H. E., *Am. J. Physiol.*, 1954, v178, 148.

2. Hegnauer, A. H., Schriber, W. J., Haterius, H. O., *ibid.*, 1948, v161, 455.

3. Gaddum, J. H., *Nature*, 1945, v156, 463.

4. Finney, D. J., *Probit Analysis*, Cambridge University Press, 1947.

Received October 11, 1957. P.S.E.B.M., 1958, v97.