

there was no microscopic difference. The testes were undamaged, with rare exceptions.

Results, Chronic Toxicity. When the gains in weight were analyzed for the experimental and control animals for the first 24 weeks and for the first year, the differences were not statistically significant for any group. During the fast growing period individual growth curves of litter mates were enough alike to be considered identical. Growth curves of the experimental groups showed no significant deviation from the control, or from each other.

Each of the 4 rats which died during the first year was from a different group, therefore, their deaths were not related to treatment. During the second year deaths were distributed over the whole period and could not be attributed directly to the effect of the palmitates. At the termination of the experiment no group had a death rate greater than that of the control.

Histopathological study similar to that of the subacute toxicity series was made of the tissues of 36 of the 60 animals and showed no outstanding gross or microscopic difference between any of the experimental groups and the control group, nor were there any distinct lesions attributable to or prevented by the palmitates. The one group of rats which did differ slightly from all the others was that fed heat-treated lard without the added palmitates. In this group, the livers usually had a slight brown or chocolate tint rarely

seen in the other groups. Microscopically, lymphocytic infiltration more frequently accompanied the small amount of focal renal tubular atrophy seen equally in all the groups, testicular atrophy was greater in degree than in all other groups, and lung involvement by chronic infectious processes and by lymphosarcoma was less frequent than in the rats whose diet included lard with added palmitates or unheated lard. However, an analysis of these data from the small number of animals in this experiment does not show a statistically significant difference.

Hematological studies made at intervals during the first year of the experiment showed no toxic effect on the blood from any of the chronic dosages of the palmitates.

Summary. When l-ascorbyl palmitate and d-isoascorbyl palmitate were fed subacutely for 9 months in concentrations of 2% and 5% of the diet, only the 5% levels were toxic. The growth rates of rats on the 5% levels were significantly retarded and bladder stones were produced in 2 animals on the 5% l-ascorbyl palmitate. d-Isoascorbic acid in a concentration of 1% of the diet had no deleterious effect. Chronic toxicity studies for 2 years indicate that l-ascorbyl and d-isoascorbyl palmitate are not toxic in concentrations of 0.25% (2500 p.p.m.), or less, of the total diet of rats. Heat-treating fresh lard containing the palmitates before adding it to the diet had no effect on toxicity.

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Use of Thermocouples for Determination of the Rectal Temperature of Rats.

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When measurements of the rectal temperatures of rats were made in this laboratory with thermometers or with thermocouples while the animals were held in the investigator's hand, the readings were unstable and frequently changed by as much as one degree

centigrade during the space of a few minutes. The results were also unsatisfactory when mechanical holders made of wire mesh were used, since the rats became unduly excited. To avoid these difficulties a method has been devised, using thermocouples, for taking the

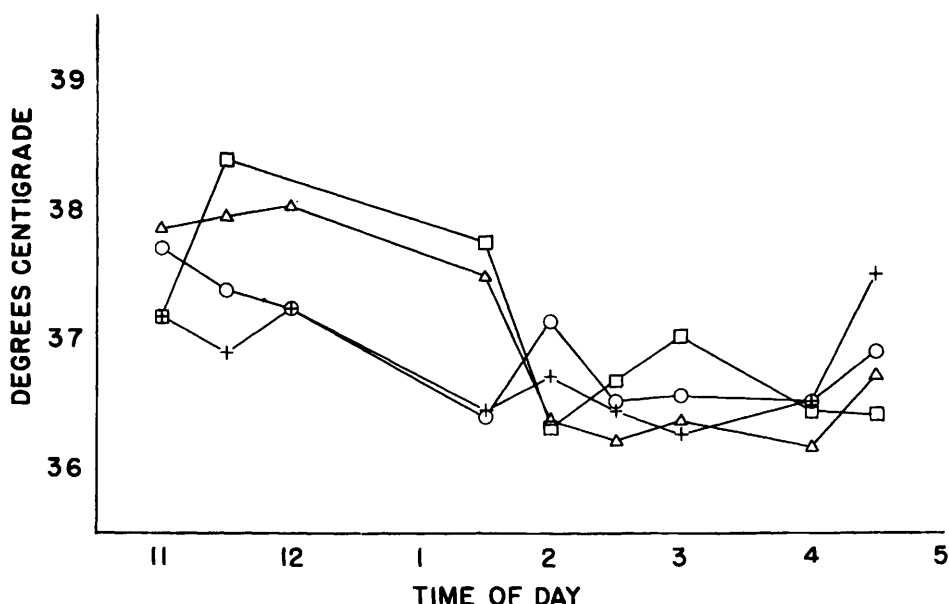


Fig. 1.
Body temperatures of 4 normal rats taken at intervals during the day.

temperatures of rats which are free in their cages and are neither excited nor subjected to a reduced rate of heat loss.

The thermocouples are made from 20 inch lengths of enamel and cotton covered iron and constantan wires, B & S gauge No. 30, which are cleaned and fused together at one end. The junction is then covered with a bead of hard solder about 2 mm in diameter which is smoothed with a file, and a $1\frac{1}{2}$ inch length of rubber catheter tubing, size No. 8 French, is passed over the wires and pulled down tightly against the solder bead. A 10 mm length of rubber tubing, $\frac{7}{32}$ inch outside diameter, $\frac{1}{8}$ inch wall, fitted over the other end of the catheter tubing, serves to anchor the end of a 15 inch length of light steel helical pull spring, $\frac{1}{4}$ inch in diameter, through which the lead wires pass to the outside of the cage. The purpose of this spring is to protect these wires from attack by the rat.

It is important that proper attention be paid to the gauge of the thermocouple wires and to the size of the catheter tubing. If the assembled junction is too limber it will be forced out of the rectum during defecation, and if it is too stiff it will cause ulceration and perforation of the colon. The

stiffness should be regulated by proper choice of the catheter tubing, and not by the gauge of the wires, which should be quite fine.

The thermocouples are attached outside the cage with silver solder to heavier wires of iron and of constantan which lead to a selector switch* making it possible to put a number of rats on test at the same time. The connections with the switch should be enclosed in a box to protect them from air currents.

The wire leading from the constantan side of the selector switch is attached to the constantan side of another thermocouple which is immersed in a reference bath of oil. This bath is mechanically stirred and electrically heated to a temperature of about 38°C , and it contains a calibrated thermometer. The iron sides of the reference junction and of the selector switch are attached through a double pole switch to the terminals of a sensitive galvanometer (5.50 u v per mm, internal resistance 2.1 ohms) and a precision wound variable resistance with a total value of 70 ohms is introduced into the lead from

* Selector switches designed for use with thermocouples are available commercially and are preferable to the ones generally used in electronic equipment.

the selector switch so that the sensitivity of the galvanometer can be adjusted.

After calibration, this circuit will measure the differences between the temperatures of the rats and that of the reference bath to $\pm 0.05^\circ\text{C}$. Each junction must be individually calibrated and will serve during daily use for about 10 days, failure being caused by rusting of the iron wire near the tip.

Specially designed potentiometers for use with iron-constantan thermocouples and containing automatic reference junction compensators are available commercially. Instruments of this type will afford greater convenience of measurement, but less sensitivity, than the circuit which has been described.

For use, the junctions are lubricated and inserted rectally to a depth equal to the length of the catheter tubing, and the end of the steel spring is firmly fastened with adhesive tape to the base of the rat's tail, which is first covered with a layer of gauze to minimize irritation. The adhesive tape is then covered with a piece of 40 mesh brass

gauze (about $2\frac{3}{4} \times \frac{5}{8}$ in. after the edges have been doubled over) which is held in place with 2 or 3 turns of wire.

After insertion of the thermocouples, the rats are returned to their cages, and the first readings may be taken about 30 minutes later. The junctions may be left in place for considerable periods of time. In the severest test to which the apparatus has been put, the temperatures of 9 rats were taken over 10 7-hour periods during 13 consecutive days. When the rats were sacrificed at the end of this time no lesions of the rectum or anus were found. Temperatures taken on a typical day are presented in Fig. 1.

Summary. 1. An apparatus for the measurement of the rectal temperatures of rats while they are free in their cages has been described. 2. An observed instability of readings which was presumably caused by reduction of heat loss or by excitation is avoided with this technic. 3. Typical results obtained at intervals during the day have been presented.

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Blood Concentration of P-chloro-xyleneol in Man Following Parenteral, Percutaneous and Rectal Application.*

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It has been shown^{1,2} that halogenized phenols and especially p-chloro-xyleneol (3,5-dimethyl, 4-chlorophenol, referred to subsequently as CX), and its derivatives exert a chemotherapeutic effect in man, in urogenital and general septic infections. Because of local irritation large amounts of these sub-

stances cannot be administered parenterally. We have, therefore, availed ourselves of experience gained in estrogenic hormone therapy³ and applied CX percutaneously. Concurrently, CX is introduced rectally. In this paper it will be shown that free CX appears in blood of patients treated with CX by various routes of administration. CX was determined in blood according to Zondek *et al.*⁴

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¹ Zondek, B., *Nature*, 1942, **149**, 334.

² Zondek, B., *J. Urology*, 1942, **48**, 747.

³ Zondek, B., *Klin. Wschr.*, 1929, **48**, 2229; *Schwz. Med. Wschr.*, 1935, **65**, 1168.

⁴ Zondek, B., Shapiro, B., and Hestrin, S., *Bioch. J.*, 1943, **37**, 589.