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A Satisfactory Apparatus for Study of Analgesia in Mice

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The white mouse is a suitable animal for the study of the threshold to induced pain because if dropped upon a heated surface it will sharply withdraw its paws when the sensation of heat is succeeded by pain, the time lapse before this withdrawal being quite constant in individual animals. The only difficulty in our experience has been to obtain a constant and uniformly heated surface upon which to drop the mouse, a handicap now overcome through the development of the herein described apparatus, which is a modification of an arrangement discussed with one of us (H. B.) by N. B. Eddy, of the National Institutes of Health, who based his method upon that described by Woolfe and MacDonald (1).

The apparatus, shown in Fig. 1, consists of a copper teakettle, the large opening of which is sealed with a copper plate and the spout of which is con-

nected with a long glass condenser through a tightly fitted cork and a copper cylinder soldered into the spout. The kettle is heated by a 600-w element operated through an adjustable bimetallic relay system and is about two thirds filled with a mixture of equal parts of ethyl formate and acetone. The mixed fumes from the ethyl formate (bp, 54°-55.5° C) and acetone (bp, 55.5°-55.8° C) are returned from the condenser to the kettle, and the temperature of the soldered-in copper plate in the top of the latter is maintained uniformly at 54°-55° C, which is just the pain temperature threshold of the mouse.

To keep the mouse in contact with the hot plate during "pain-point" determination, a glass cylinder with a cover is fixed on top of the plate. The simultaneous lifting and licking of both forefeet have served us as the most reliable "pain-point," all mice invariably showing this sign within 15 sec after being put on the plate. In our experience any agent deferring the "pain-point" beyond 15 sec may be considered an analgesic.

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Stress and Ketone Body Metabolism¹

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A clue to the role of fat in the metabolic adjustments of man to systemic stress has been provided by a review of data on ketonuria observed during Army ration trials and nutrition surveys. As a part of the nutritional and metabolic assessment of the troops taking part in the trials and surveys conducted in the period 1944-50, specimens of urine were collected for routine testing by one or another modification of Rothera's method (1) for detecting the presence of nitroprusside positive substances. The positive reactions, which were identical with those originally described by Rothera (1), were qualitatively graded: trace and 1 to 4+. In general the results have been reported as percentages of the tested samples that were positive at any given time (to be called here "per cent ketonuria").

The specimens of urine were collected under a variety of conditions. In the nutrition surveys, the specimens represented random samples. Occasionally similar samples were taken on ration trials. Usually,

¹ The opinions expressed in this paper are those of the authors and do not necessarily represent the official views of any governmental agency.

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³ To Jack Bollerud, who stimulated our interest in the ketonuria observed during cold weather ration trials, and Everett Bowden, of the Arctic Aeromedical Laboratory, we are indebted for supplying considerable unpublished data on ketonuria occurring during Alaskan ration trials. We wish to thank R. E. Johnson for his assistance in preparing this paper.

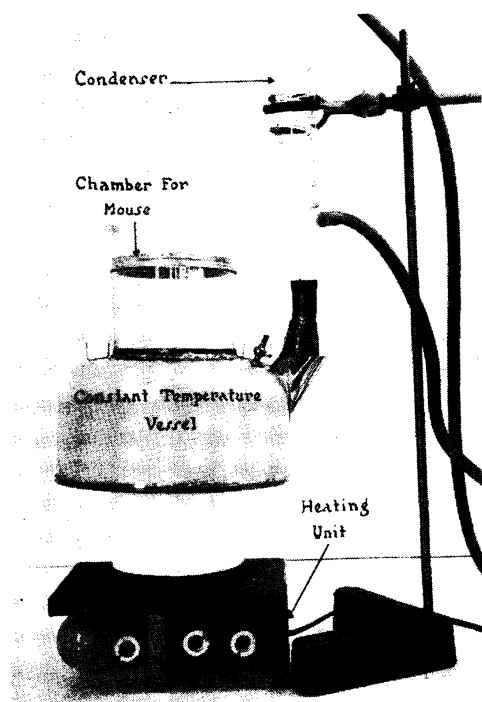


FIG. 1. Apparatus for study of analgesic threshold in mice.

however, on such trials specimens were collected according to a fixed plan, which was followed both during the control periods and also when the troops were living in the field under various simulated tactical and survival situations. According to the protocols, 24-hr specimens of urine, two 12-hr specimens per day, or two daily random specimens obtained early in the morning or late in the afternoon were collected from each subject. In all instances the samples were analyzed daily by trained personnel.

The stresses to which the subjects of a ration trial were exposed were not noxious; i.e., they did not cause tissue damage. They were, however, sufficiently severe to require bodily adjustments. When the activities of the trial were those of a simulated tactical situation, three types of stress were encountered: psychological (such as the routine of the trial, living under somewhat primitive conditions, and preparing and eating packaged rations); climatic (heat and cold); and muscular (marching fully equipped over various terrains). In cold climates the exercise also included preparing the camp site, and when on the march the men frequently dragged heavily laden sleds. When a survival situation was simulated, the stress of muscular exercise was not encountered. In the case of nutritional surveys, the chief stress experienced was probably climatic.

A study was made of the occurrence of ketonuria among random specimens of urine collected during nutritional surveys and control specimens obtained from subjects prior to the beginning of various ration trials. The analysis revealed that ketonuria tended to be more common in cold climates (Alaska and Canada) than in temperate or tropical climates (Colorado, Hawaii, and the South Pacific Islands). In six trials conducted in cold climates per cent ketonuria was 0, 6, 6, 8, 12, and 22. In six nutritional surveys and ration trials in temperate and tropical climates, per cent ketonuria was 0, 0, 0, 0, 2, and 2.

During the course of the ration trial, it was found that the daily incidence of ketonuria followed a characteristic curve, which will be designated "curve of per cent ketonuria." Three phases were generally detectable in this curve: low levels during the control period of the trial, an ascent to a maximum a few days after beginning the field period, and a decline to control levels before the termination of the field period. These phases are illustrated in the four curves of Fig. 1.⁴ The subjects of these Camp Shilo Trials, who had been acclimatized to the winter climate of Florida, were abruptly transported by air to Camp Shilo, Manitoba, and placed in bivouac under simulated survival conditions. After 12 days in the field, they were transferred to warm barracks for 3 days (recovery phase). The troops performed no regular tactical exercises. The estimated caloric balances for the four groups were: I, -1,770; II, -1,290; III, -1,230; and IV, +840 cal/man/day. Each group subsisted on a different ration. Other details of these

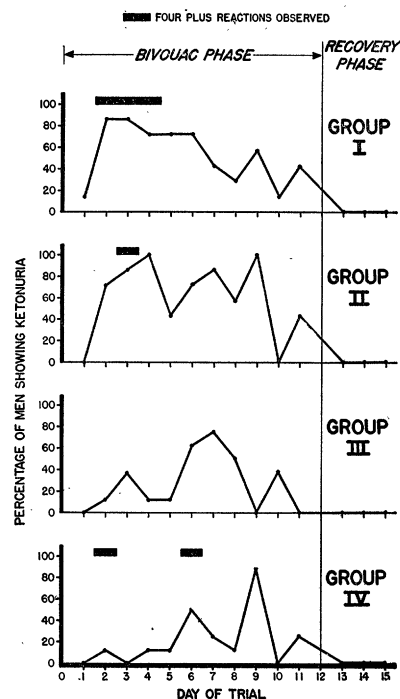


FIG. 1. Percentage of men showing ketonuria each day during Camp Shilo Trials, 1948. The bivouac phase indicates period when subjects were living under simulated survival conditions. During recovery phase men lived in heated barracks. The horizontal bars designate days on which at least one subject excreted urine that tested 4+ by the Rothera method. The estimated caloric balances for the four groups were: I, -1770; II, -1290; III, -1230; and IV, +840 cal/man/day.

trials have been published elsewhere by Bly, *et al.* (2).

The time required for the curve of per cent ketonuria to reach a maximum varied in different ration trials from 1 to 8 days. Such a variation was evident in the Camp Shilo Trials (Fig. 1). Analysis of the various data suggested that the caloric balance was one factor governing time to maximum per cent ketonuria. For example, in the Camp Shilo Trials, the more negative the caloric balance, the more rapidly did the curve of per cent ketonuria reach a maximum. When similar troops were exposed to field conditions in successive trials, it was found that there was regularly less ketonuria in the second trial than in the first.

A relationship between ketonuria and muscular exercise was clearly demonstrated in the Prince Albert Trials (3). In this trial late-afternoon urinary specimens (collected after a day of marching) more frequently exhibited ketonuria than did morning urinary specimens (collected after a night's rest). In these trials, however, the curve of per cent ketonuria was superimposed on the diurnal cycle attributable to the influence of exercise. That muscular exercise is a cause of ketosis has been established by many investigations (4-9). The explanation of this exercise ketosis has not, however, been satisfactorily worked out.

The curve of per cent ketonuria is independent of

⁴ Unpublished data from the Army Medical Nutrition Laboratory.

the composition of the food consumed and of caloric expenditure. These inferences follow from the fact (a) that ketonuria occurred in troops during the testing of a wide variety of rations and (b) that ketonuria occurred both when the troops performed hard work and when they did not (as in trials on survival rations). These observations further suggest that depletion of liver glycogen did not occur. What, then, may have been the cause of the ketonuric phenomena? The hypothesis is offered that the curve of per cent ketonuria is an expression of the general adaptation syndrome—i.e., that it represents adaptation to systemic stress (10). That cold is the principal stress involved is suggested by the observation that ketonuria is more frequent in cold than in warm climates. Muscular exercise may be a stress involved in some of the trials, for the reduction in ketonuria on exposure to successive trials in which the subjects did work suggests the development of resistance through training. Winkler and Hebelers (9) have shown that trained athletes do not develop exercise ketosis. It is also possible that the curve of per cent ketonuria

represents the development of a state of crossed resistance (10); i.e., adaptation to cold facilitates adaptation to muscular exercise, and vice versa. Furthermore, Selye (10) has found that fasting intensifies the alarm reaction produced by many stressors. It may be, therefore, that the inverse relationship between time to maximum per cent ketonuria and caloric balance is an expression of such intensification.

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Book Reviews

Dating the Past: An Introduction to Geochronology. 2nd ed. Frederick E. Zeuner. New York: Longmans, Green, 1951. 474 pp. and 24 plates. \$5.50.

This important work, first published by Methuen in 1946, is now available in a new edition, printed in England but bearing an American imprint. Virtually identical with the first edition in number of pages and illustrations, it nevertheless deserves to be called a second edition, for it has been revised with some thoroughness. Several completely new sections (e.g., on radioactive dating of deep-sea cores) have been added; others (such as the paleolithic archaeology of South Africa) have been completely rewritten, and new illustrations and correlation tables substituted for many old ones. It is clear, however, that the revision was accomplished as cheaply as possible—by extensive reprinting from type of the original edition, and by sacrificing perfectly good illustrations in favor of newer but not necessarily better ones. The tempo of research in the subject is partly responsible, along with considerations of economy, for a somewhat scattered treatment: much last-minute information (on radiocarbon dating, the fluorine method, etc.) is included in the Notes rather than in the body of the text, but some of the Notes are reprinted without essential change from the first edition, and others constitute notes on the Notes.

Owners of the first edition will probably not need to buy the new one, but this edition is nevertheless welcome. For those who will now make the book's acquaintance for the first time, a brief appraisal may

be necessary. It is, beyond any doubt, an exceedingly useful, interesting work. Professor Zeuner is a tireless bibliographer, and he has covered in a creditable manner the whole enormous range of geochronologic measurement—from tree-ring and varve counting through Pleistocene stratigraphy (with emphasis on paleolithic archaeology) to radioactive estimates of the age of the earth and of the universe. As a sort of annotated bibliography it is invaluable. Even though it does not pretend to be exhaustive, in the field the reviewer knows best (the Pleistocene) there are few references that are pertinent, and hardly any that are significant, that cannot be found by means of this book and the sources it cites.

In other respects, however, the book is not entirely satisfactory. Complete objectivity in reporting so large and controversial a field is probably not attainable, or even desirable, for, where facts are subject to diametrically opposed interpretations, impartiality can mean only dullness and lack of critical acumen. Zeuner's treatment is by no means impartial, but the reviewer is aware that his dislike of some things in the book arises less from its partisanship than from a belief that the partisanship is mistaken. Hence, while *Dating the Past*, like its companion volume *The Pleistocene Period* (London: Bernard Quaritch [1945]), is full of special pleading, it seems a little unfair to condemn it, as an earlier reviewer did, as "a sustained exercise in special pleading." Our knowledge of Pleistocene stratigraphy is so wretchedly inadequate that any attempt to organize it into a con-