to CO_2 fixation. This incorporation, conceivably by direct CO_2 fixation (*11*) or via pyrimidine precursors such as aspartic acid (*12*) and lactic acid (*13*), may be adequate to explain the isotope content of the nucleic acids of the normal liver but not of the hepatoma.

The conclusion that the uracil has entered into nucleotide formation is supported by the results of ion exchange fractionation. The Dowex I formate forecuts, containing the impure purine bases, exhibited activities of *ca.* 10–15 cpm/mg of base, whereas the activity of the main cytidylic and uridylic acid fractions was 170 and 230 cpm/mg of base, respectively. The absence of uptake into the purine bases and the approximate correspondence between observed pyrimidine nucleotide isotope content and that expected (*ca.* 250 cpm/mg base) on the basis of nucleic acid specific activity suggest a reasonably direct utilization of the uracil. The significance of the radioactivity present in other fractions awaits further purification.

On the basis of the detailed experiment reported, as well as of a number of preliminary tests, it appears probable that AAF carcinogenesis involves an alteration of the pattern of nucleic acid metabolism of the liver, one aspect of which involves the utilization of preformed uracil. Although the basic significance of this observation remains to be established, it appears likely that this metabolic alteration underlies the striking ability of thiouracil to inhibit hepatoma formation by AAF. The work of Kidder *et al.* (*14*) indicates that another nucleic acid antagonist, 8-azaguanine, depends for its inhibitory action (in *Tetrahymena geleii*) on the physiological state of the test organism.

Studies are in progress to determine whether the altered metabolism observed in the hepatoma is shared by other growing systems such as regenerating liver and embryonic tissues. The rapid catabolism of uracil has also indicated the desirability of investigating possible exchange reactions around the ureido carbon.

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Comments and Communications

Development of Strains of Albino Mice with Predictable Susceptibilities to Audiogenic Seizures[1]

LABORATORY mice have some advantages over rats for the study of audiogenic seizures. The level of incidence of seizures is highly uniform within specific strains (*1–5*), so that animals with known susceptibilities can be selected for experiments. The incidence of otitis media, which may be a complicating factor in rats (*6–8*), is very low (*9, 10*). The types of seizures and stages in their genesis have been described (*4, 11, 12*). Apparatus has been developed for the control of the stimulus situation (*4, 13*), so that duplication of this factor is assured. And, finally, mice require much less space for rearing than do rats.

A serious objection to the use of mice as test animals in these studies, however, has been that they die in clonic-tonic seizures (*1, 3–5, 10*). To overcome this difficulty and, at the same time, to reduce the variability in response of individual mice at specific ages (*4*), we have had in progress for over two years a program of selection and progeny-testing of mice for specific susceptibilities to audiogenic seizures. The strains thus produced have been developed from an originally random albino stock and are variously inbred and outbred. All records of seizures are available from the start of the selection, because no mice have been saved for breeding without routine testing. As these strains may prove of value to other research workers interested in this aspect of rodent physiology and psychology, the characteristics of the strains that have been produced are briefly described herein. Breeding pairs of any of these strains of mice will be supplied to interested individuals for testing on request, within the limits of our resources.

Mice of the first strain, when tested daily from 15 to 50 days of age, have a very high incidence (90–100%) of clonic-tonic seizures, but they rarely die in the seizures. In the original stock there was one death for every 1.5 clonic-tonic seizures. At present there is only one death in approximately 250 seizures. This figure is by no means the maximum, because the testing of mice for breeding is routinely discontinued at

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50 days of age, when they are still highly susceptible. These animals continue to have seizures after that, if they are tested.

Mice of the second strain, when tested daily from 15 to 50 days of age, also have a high level of incidence of seizures, but the seizures are of the clonic type only. In this case, too, the mice do not die, because this type of seizure is rarely fatal (*11, 12*). In both these strains the latent periods of the seizures (i.e., the time elapsing between the start of the stimulus and the start of the seizure) are quite short (1–10 sec; av 5.3 ± 1.3 sec). In the original stocks the average latent period was 35 ± 2 sec. Thus testing is greatly expedited in these strains. The reduction in the latent period is probably the result of the increased susceptibility to seizures (*14, 15*).

Mice of the third strain, when tested from 15 to 50 days of age, have seizures at the 90–100% level between 17 and 24 days of age, but have 0–5% seizures between 30 and 50 days of age. These animals are valuable particularly in maturation studies, because the same animal is susceptible at one age and nonsusceptible only a few days later.

Mice of the fourth strain—by far the most difficult to produce—when tested similarly, have a very low incidence (5–10%) of seizures and have a large number of individuals that have no seizures at all. In the 22 offspring of one pair of these mice, for instance, 16 of the animals had no seizures. These nonsusceptible mice are valuable for comparison with the highly susceptible mice and for use in studies in which seizures are undesirable.

Details of the selection procedures and development of these strains will be presented elsewhere.

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A Metabolic Cage

THE Krebs tricarboxylic acid cycle is frequently referred to as a "furnace" in which intermediates are oxidized to CO_2 and H_2O. The initiated, who know enough not to take such statements literally, automatically include the subsequent electron transfer reactions, in which the ultimate acceptor is oxygen, as part of the system. Many students, however, have difficulty in understanding the relations of the two sets of reactions. As a means of demonstrating these relationships more clearly, the author has constructed a model (Fig. 1).

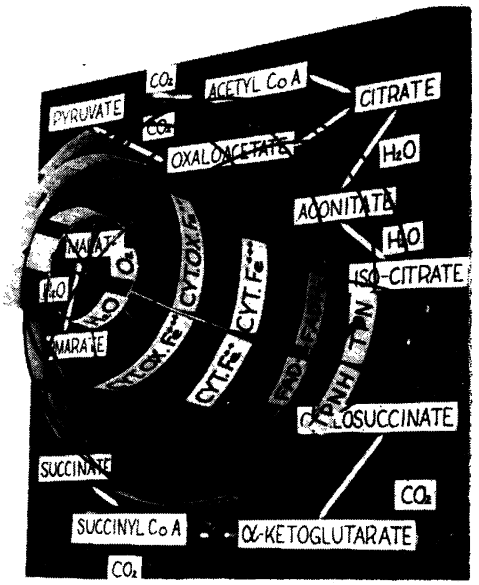

FIG. 1.

The reactions of the tricarboxylic acid cycle are represented as proceeding in a clockwise direction. Nonoxidative reactions are indicated by white arrows pasted flat to the base. Oxidation reactions in the cycle are indicated by raised red arrows which symbolize the loss of electrons. The transfer of electrons to the pyridine nucleotides is indicated by blue arrows, which are bowed toward the base. The series of electron transfers from the pyridine nucleotides, to the flavins, cytochromes, and finally to oxygen, is represented by the ascending groups of cards, each set with its red and blue arrows to indicate the electron transfers. One such group, starting with the isocitrate-oxalsuccinate: TPN-TPNH couple, faces the camera. Another series, beginning with the malate-oxalacetate: DPN-DPNH reaction, is shown from the rear. These two series illustrate the relationship adequately; hence the others have not been completed on the model. Blank cards are placed over the succinate-fumarate arrow as an admission that we do not as yet know all the answers.

To avoid confusion, many reactions and other details have been omitted. Thus, the transamination reactions, linkage with glycolysis, fatty acids, etc., could easily be added if desired. Likwise metals, cocarboxylase, phosphate, adenylic nucleotides, etc., are not depicted. Once a student grasps the central ideas, he has little difficulty adding these details to the conceptual superstructure. The cage does bring out the