the mutant strain. Whatever the mechanism is for the excretion of adenine by the mutant strain, it is not *per se* responsible for the resistance to DAP(1).

Summary. The mechanism of excretion of adenine by the mutant *dap-r-3* of *Salmonella typhimurium* selected for resistance to DAP was studied. The mechanism for control of purine biosynthesis by feedback inhibition is unaffected in this mutant as indicated by (1) inhibition of AICA synthesis in sulfadiazine-inhibited prototrophic strains *dap-r-3* and *LT-2* by hypoxanthine and adenine; and (2) inhibition of AICA synthesis by adenine and its nucleoside in nonproliferating suspensions of *Escherichia coli B 96/1/dap,* a DAP-resistant mutant derived from a purine requiring auxotroph *B 96/1* resembling *dap-r-3* mutant in its properties. In general, more adenine was required for feedback inhibition in the resistant mutant than in the parent strain. The differences have been ascribed to poor utilization of adenine by the resistant strain.

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Thyroid Activity and Heart Rate.* (27179)

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The increase in heart rate occurring in artificially induced hypothyroidism apparently results from local changes in the heart in addition to the indirect effects of increased metabolism in other tissues. This is suggested by the increased oxygen consumption found in myocardial tissue(1,2). Furthermore, elevated sinus rate after administration of thyroid or thyrotropic hormone, thyroxine, triidothyronine and some of its derivatives persists when the heart muscle is beating spontaneously in the isolated state(3-8). In the hypothyroid state, with decreased metabolic rate, heart rate may be decreased but this is not necessarily the case(9). The present study was performed to compare heart rates in intact animals and beat rate of isolated heart muscle preparations of rats treated with l-thyroxine or l-triiodothyronine or thyroidectomized with radioactive iodine; a preliminary report was previously published in abstract form(10).

Methods. Wistar strain rats of both sexes weighing 150 to 340 g served as experimental animals. Test rats and corresponding control animals were of the same age and, at the beginning of experiment, of the same size. Heart rate determinations in intact rats were performed electrocardiographically in a wooden box divided by partitions into 10 sections, each for one animal. Each rat stood on 2 metal plates, one under the front legs, the other under the hind legs. The animals were allowed to become quiet for a half hour before any recordings were performed. Re-

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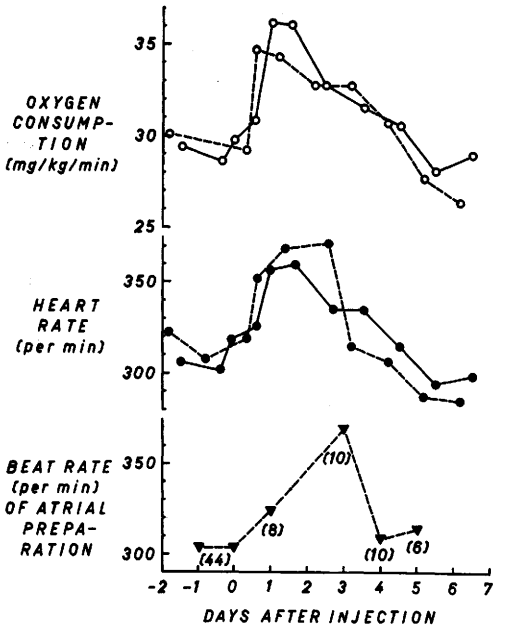

FIG. 1. Mean oxygen consumption of 20 rats (○——○ thyroxine; ○- - -○ triiodothyronine). Mean heart rate of same animals (●——● thyroxine; ●- - -● triiodothyronine). S.E. at any point $< \pm 10$ beats/min. Beat rate of atrial preparations at 37°C before and 1 to 5 days after inj. of triiodothyronine, 2.5 mg/kg b.w. (▲- - -▲); No. of preparations indicated in parentheses.

cording was then made several times of each animal and the lowest observed heart rate was taken as the control value. After a few trials the animals became accustomed to the procedure and remained calm in the box. Spontaneous sino-atrial rate *in vitro* was measured at 37°C with a piezo-electric crystal on isolated right atrial preparations beating in modified Locke's solution in an isolation chamber provided with a continuous oxygen stream, as described previously(11). L-thyroxine (British Drug) and l-triiodothyronine (Glaxo) were used as 1:1000 (w/v) solutions in distilled water containing equal amounts of sodium carbonate and administered subcutaneously as single injections. The dose of thyroxine was 10.0 mg/kg b.w. and that of triiodothyronine 2.5 mg/kg b.w. Control injections were made with 1:1000 sodium carbonate solution in equal volumes without changes in heart rate or oxygen consumption. Radiothyroidectomy(12,13) was performed by a single injection of 500 μc of I^{131} two to 4 months before experiment. Histological study of the thyroid glands was not routinely done; observations on a comparable series have been reported(14). Oxygen consumption of the rats was determined by a closed circuit method(15) on 5 animals simultaneously.

Results. Fig. 1 shows the close parallelism between heart rate and oxygen consumption observed in rats treated with l-thyroxine and l-triiodothyronine. Durations of increased heart and metabolic rates were practically equal after thyroxine and triiodothyronine injections. The beat rate of isolated atria of triiodothyronine-treated rats which were killed 1 to 5 days after injection was very close to that recorded in intact animals. Duration of the period of elevated heart rate was the same both *in vivo* and *in vitro*. There were no consistent differences either in heart rate or oxygen consumption between radiothyroidectomized and normal control animals. During a control period of 5 days the daily mean heart rate of 20 control animals ranged between 272 and 281 beats per minute and that of 20 I^{131}-treated animals between 258 and 281. Oxygen consumption of the normal group (mean of daily determinations during 5 days) was 27.2 $\pm$ 0.5 mg/kg b.w./min and that of the hypothyroid group 1.8 $\pm$ 0.6 mg less. There were, however, days on which equal results were obtained. A striking difference was found in the beat rates of isolated atria (Table I). The rate of hypothyroid atria was less than 60% of that of control preparations.

The body weight of I^{131}-treated animals remained unchanged after I^{131}-injection while controls of equal age and size gained an average of 25% in weight. The relative heart weight at time of experiment in a series of 20 hypothyroid male rats was 0.265 $\pm$ 0.004 (S.E.) % of body weight; it was 0.024 $\pm$ 0.006% greater in control animals. In

TABLE I. Beat Rate of Atrial Preparations of Normal and I^{131}-Treated Rats at 37°C.

	No. of preparations	Beat rate (per min.) Mean $\pm$ S.E.
Normal controls	40	300 $\pm$ 9
I^{131}-treated	30	171 $\pm$ 7
Difference		129 $\pm$ 11

equal series of female rats there was only a 0.013 ± 0.007 % corresponding difference.

Discussion. In rats injected with thyroxine or triiodothyronine *in vivo* oxygen consumption and heart rate were closely parallel. The beat rate increase of isolated atria of triiodothyronine-treated rats at 37°C paralleled the heart rate *in vivo* both in magnitude and duration. In the present series no significant differences in duration of the effects of l-thyroxine and l-triiodothyronine were found in contrast with other studies showing triiodothyronine to have shorter action than thyroxine(16,17).

Radiothyroidectomized rats gave a different result. In spite of equal heart rates of control and hypothyroid rats, *in vitro* studies indicated a difference in the hypothyroid heart. Previous experiments in rats have shown impaired contraction force in hypothyroid rat atria, especially at low temperatures(13), and quantitative differences in response to epinephrine(18). A requisite of the rat atrial muscle for quantitatively normal function in the isolated state seems to be an adequate thyroid influence before isolation. The present results suggest that the heart of the resting hypothyroid rat is regulated by nervous or humoral factors, or both, to beat at a higher rate than it would do if its beat rate were determined alone by its spontaneous pacemaker activity. This is on the assumption that the difference between normal and hypothyroid preparations is more than a different sensitivity to experimental conditions *in vitro*. To elucidate which factors are involved in this regulation further studies are needed. One possible factor is anemia, frequently associated with hypothyroidism(19). Possible effects of irradiation of the parathyroids by the I^{131} have not yet been investigated. In human hypothyroidism heart rate is not necessarily decreased (9). In the present rat series the heart weights of hypothyroid rats were equal to or slightly smaller than those of control animals, while increased heart size is a regular finding in hypothyroid patients(18). This might indicate differences between human and artificially induced rat hypothyroidism. In hypothyroidism there is apparently more involved than a quantitative change in metabolic level. Different functions are affected in a way which disturbs the harmony of the organism and limits its adaptive possibilities.

Summary. Beat rate determinations were made of the hearts of euthyroid, thyroxinized and triiodothyroninized rats *in vivo* and of atrial preparations of correspondingly treated (except for thyroxine) animals *in vitro*. A close parallelism was found between *in vivo* and *in vitro* experiments. Durations of the effects of thyroxine and triiodothyronine were equal. In radiothyroidectomized animals the rate of beat in isolated atria was less than 60% of that of euthyroid atria although no significant differences were observed in the heart rates of intact hypo- and euthyroid animals.

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Uptake of Radioactive Zinc and Manganese in Damaged Rat Liver. (27180)

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The effect of hepatic damage upon the metabolism of various trace metals has not been well defined. Vallee(1) reported decreased serum and hepatic zinc levels and increased zincuria in patients with post-alcoholic cirrhosis. Butt(2) found decreased hepatic manganese content in patients with hepatic necrosis. On the other hand, Smith *et al.* (3) demonstrated an increased hepatic uptake of Mg^{28} after hepatotoxic doses of CCl_4 in the rat. The present report concerns the uptake of two trace metals, Zn^{65} and Mn^{54} by normal and CCl_4 damaged rat livers.

Methods. Zn^{65} Uptake. A solution of Zn^{65} supplied as the carrier free chloride, was diluted with demineralized water to contain 0.2 μc of zinc per ml and the pH was adjusted to 6.0. Nineteen Holtzman, female, albino rats, weighing 250 g ($\pm$ 3 g) were given 0.5 ml CCl_4 by subcutaneous injection. As a control, an equal number of female rats were injected subcutaneously with 0.5 ml of 0.9% sodium chloride. Forty-eight hours later, 1 ml of the Zn^{65} solution was injected subcutaneously. Animals were sacrificed in equal groups at 1, 3, and 9 hours following injection of the isotope. Tissues were removed, briefly dipped in N. saline to remove blood from the surface, and dried at 100°C for 24 hours. After drying, the tissues were passed through a tissue mill and weighed aliquots were counted in a scintillation well. Whole organ wet weights were recorded for several rats from both control and CCl_4 groups. No significant difference was noted between the two groups for any specific organ.

Mn^{54} Uptake. Mn^{54} supplied as the carrier free chloride was diluted with demineralized water to contain 0.2 μc of manganese per ml and the pH was adjusted to 6.0. Twelve Holtzman, female, albino rats, weighing 237 g ($\pm$ 3 g) were injected subcutaneously with 0.5 ml of CCl_4. As a control an equal number of female rats were injected subcutaneously with 0.9% sodium chloride. Forty-eight hours later, 1 ml of Mn^{54} solution was injected subcutaneously. Animals were sacrificed at 3 hours following injection of the isotope. At sacrifice, tissues were removed and treated in a manner similar to those of the zinc experiment.

Results. Zn^{65} Uptake. Results are reported as % uptake per gram of dry weight, *i.e.*,

$$\left(\frac{\text{NCPM/g dry tissue}}{\text{NCPM injected}}\right) = \% \text{ uptake per g dry wt.}$$

No significant difference in uptake of Zn^{65} in the liver or other tissues was noted at any time period between animals injected with CCl_4 and controls (Table I). Liver tissue sections of animals injected with CCl_4 showed swelling and disruption of mitochondria, diffuse fatty infiltration and centralobular necrosis. Elevation of the dose of isotope failed to bring about any change in distribution or per cent uptake for any given tissue.

As shown in Table II, Mn^{54} uptake was significantly reduced in the livers of rats receiving CCl_4. Elevated doses of Mn^{54} failed to affect the general pattern of Mn^{54} uptake by damaged hepatic tissue.

Discussion. These data indicate that hepatic uptake of zinc is not affected by acute damage to the liver of rats. No studies on the effect of chronic liver damage on zinc uptake have been done to date which would be