The findings with aureomycin are of considerable practical clinical interest. There is undoubtedly a definite shortening of clotting time noted at the height of antibiotic therapy. While ordinarily nature provides a wide compensatory mechanism for prevention of thrombo-embolic accidents, still the coagulatory apparatus may be considered as in a metastable state, so that sudden physiological disturbances might precipitate thrombo-embolic accidents. Hence suitable prophylactic measures by use of anticoagulant drugs may be instituted.

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Body Retention of Carbon 14 from Labeled Sodium Bicarbonate[1]

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In view of the present wide usage of carbon 14 and the concern regarding possible radiation hazard involved, it is believed that certain data obtained on this subject are worth recording at this time. Bloom, Curtis, and McLean (*2*) and Armstrong, Schubert, and Lindenbaum (*1*) have previously published results indicating long term body retention of C^{14} from water soluble and insoluble carbonates. Brues and Buchanan (*4*) have reported some interesting results on the over-all metabolism of carbon dioxide.

The present experiments were designed to obtain quantitative data on $C^{14}O_2$ fixation, from which average body radiation could be calculated. Twelve mice were injected intraperitoneally with a solution containing 2.5 mg of $NaHC^{14}O_3$ and a total activity of 18 μc. The expired CO_2 from all animals was collected over varying intervals, and two mice were sacrificed for organ and tissue analysis at 24 hr, 48 hr, 1 week, 2 weeks, 4 weeks, and 3 months. The C^{14} assays were carried out on pooled blood, spleen, liver, kidney, lung, brain, small intestine, muscle, skin and hair, and bone samples. The procedures used in collecting expired CO_2 and excreta, oxidizing samples, and counting have recently been reported (*6*). The percentage of the total activity retained at a given time was calculated by difference (100% − expired and excreted C^{14}) for the first 24 hr; the activity retained after longer periods was calculated directly from organ,

[1] This work was carried out for the Atomic Energy Commission under a contract with the Office of Naval Research. Certain data reported herein were obtained in experiments carried out under a grant from the American Cancer Society on recommendation of the Committee on Growth, National Research Council.

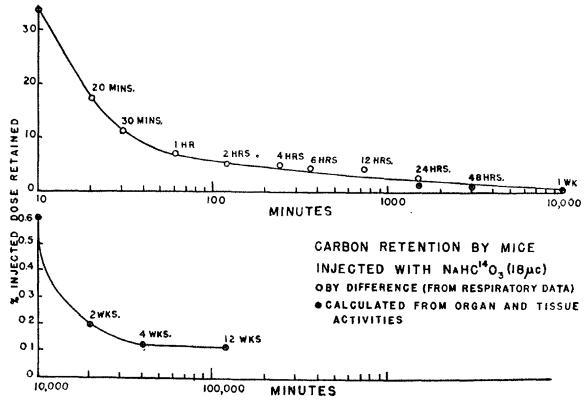

FIG. 1. Carbon 14 retention by mice injected with $NaHC^{14}O_3$.

tissue, and fluid weights, and specific activities. These results are presented in Fig. 1. If the amount of C^{14} in the body and the average energy of radiation are known, it is simple to convert such data to roentgen equivalent physical[2] (the basis for radiation tolerance calculations). With the assumption of even distribution, such calculations have been performed with regard to total body radiation and are presented in Table 1. To date we have

TABLE 1

BODY RADIATION OF MICE INJECTED WITH $NaHC^{14}O_3$ (18 μC)

Period	Body C^{14} content (integrated)		Body radiation	
	μc	% of injected dose	Total rep period	Average daily rep period
0–60 min	4.3	23.6	0.0250	
1–2 hr	1.12	6.2	0.0058	
2–4	1.00	5.6	0.0104	
4–6	0.92	5.12	0.0090	
6–12	0.86	4.77	0.0266	
12–24	0.54	2.93*	0.0333	
0–24	0.87	4.80	0.110	0.1101
24–48	0.21	1.15	0.053	0.027
1–7 days	0.18	1.00	0.1328	0.022
7–14	0.07	0.41	0.0636	0.009
2–4 weeks	0.03	0.16	0.0496	0.004
4–12	0.02	0.13	0.1613	0.003

* This value is an average of the 12-hr C^{14} level obtained by difference (100% − % expired) and the 1.37% found in the tissues at 24 hr.

Note: Tolerance does limit for a 24-hr exposure as set by Clinton Laboratories = 0.1 rep.

observed no outstanding selective accumulation of C^{14} from a gross anatomical standpoint.[3] It was observed that the rate of uptake and loss of C^{14} by the jejunum (a rapidly proliferating tissue) was significantly greater

[2] One rep or roentgen equivalent physical = 83 ergs/g of tissue. This dose is considered to produce no known effects on man when exposed indefinitely. Factor of safety is probably no more than 2 or 3 (*5*).

[3] The detailed results of these experiments, along with certain calculations as to rate constants having to do with carbon turnover, are being presented elsewhere.

than for other tissues studied. It is obviously necessary to carry this search for specificity into the finer structures of cells, organs, and bone.

When the difference in weight of a man and a mouse is taken into consideration, it is apparent from Table 1 that the average over-all body radiation from bicarbonate C^{14} is apt to be lower than the tolerance level of 0.1 rep per day for man unless high doses are administered (of the order of 5 mc if a safety factor of 10 is assumed for species variation in the biological half-life of bicarbonate C^{14}). It is of course important to study the long term retention of C^{14} from insoluble carbonates and organic molecules which enter the metabolic pathways before being degraded to carbon dioxide, prior to any final conclusions regarding hazard from C^{14}.

Experiments designed to indicate the effects of low doses of $NaHC^{14}O_3$ on the pattern of leukemia in a highly susceptible strain of mice are now under way in this laboratory.

This report should not be construed to suggest at our present state of knowledge an increase in Brues' (*3*) tentative maximum retained dose for man of 30 μc of C^{14}.

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Action of the Venom of Bothrops Atrox on Fibrinogen

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It has been shown by Laki and Mommaerts (*3*) that the conversion of fibrinogen to fibrin takes place in two stages: first, thrombin brings about some change in the fibrinogen molecules, which then polymerize to a clot. These authors have also shown that a solution containing phosphate buffer, pH 5.1, fibrinogen and thrombin, does not coagulate. Clotting occurs only after neutralization of the system with secondary phosphate buffer. The longer the thrombin and fibrinogen are incubated at the acid pH, the shorter the clotting time becomes. This shows that a primary reaction takes place even at pH 5.1, and the polymerization of the primary product, the profibrin, into fibrin takes place only at a higher pH.

The thrombin-like clotting action on blood and fibrinogen of the venom of Bothrops atrox (*1*) has been compared with thrombin under the same experimental conditions as described by Laki and Mommaerts. In these experiments the fibrinogen solution was prepared according to the method of Laki (*2*). As clotting agents, thrombin of Parke and Davis Company, a saline Bothrops atrox solution in a dilution of 1: 15,000, and a venom solution precipitated three times with acetone and heated at 50° C for 20 min, were used.

To aliquots of fibrinogen solution brought to pH 5 with phosphate buffer there was added thrombin, or the venom, or the acetone-precipitated venom solution. After various incubation times a part of the reaction mixtures was removed and neutralized with secondary phosphate to pH 7, and the clotting time was measured.

Fig. 1 illustrates the coagulation curves obtained by the three different solutions. It can be seen that venom transforms fibrinogen into profibrin faster than thrombin,

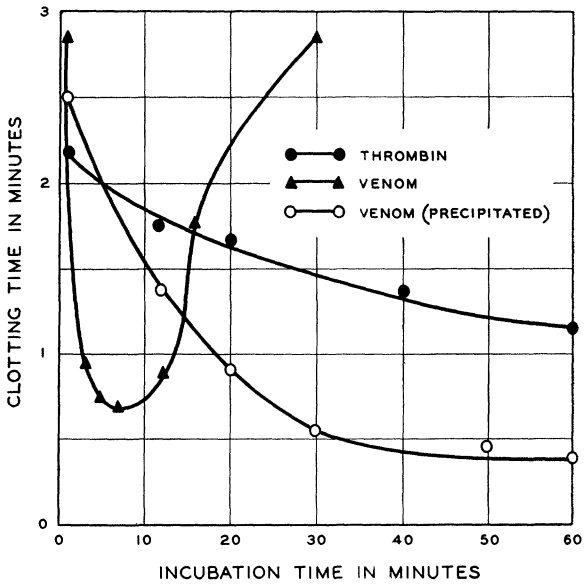

Fig. 1. The effect of incubation time on the clotting of reneutralized fibrinogen solution brought about by the action of thrombin, venom, and precipitated venom.

but after a certain time the clotting time becomes longer and longer, and finally the neutralized fibrinogen-venom-buffer system does not clot at all. Addition of thrombin to such neutralized solutions does not bring about coagulation, but if fibrinogen is added, clotting takes place. This shows that the reversal of the venom curve is caused by the disappearance of reactive fibrinogen, presumably due to fibrinolysin present in the venom. In the case of acetone-precipitated venom, the reaction is similarly fast, but the clotting time, having reached its lowest value, remains at this level.

These experiments with acetone-precipitated and heated venom solutions show that precipitation and heating eliminates, or at least reduces, the fibrinolytic action of venom, and that the clotting action of venom is not only due to its proteolytic activity but to some thrombin-like enzyme. Further details of this work will appear elsewhere.

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