enzyme content of the surrounding medium attributable to leakage from the hepatocytes. Leakage of GOT and of GPT, however, occurred at concentrations approximately 100-fold greater than those usually found in serum, but less than 10-fold greater than those that can be found in the liver, both in humans as well as rabbits after therapeutic dosages (8,9). Leakage of enzyme from cells into medium may be assumed to represent membrane injury. Direct hepatotoxins, such as carbon tetrachloride, which are known to injur cellular membranes have been shown to produce effects *in vitro* analogous to those demonstrated with CPZ (5). The significance of the CPZ effect is supported by the observation that PZ in equal concentrations, induced no recognizable degree of leakage of enzymes from the cells. Patients who receive chlorpromazine develop a high incidence (50%) of mild hepatic dysfunction (2–4) and a significant incidence (1–5%) of jaundice (1). Promazine appears not to lead to hepatic dysfunction in patients who are serially studied (9) and has been associated with recognizable jaundice with extreme rarity (1). The difference in cytotoxicity for liver slices demonstrated *in vitro* appears to parallel the *in vivo* difference of occurrence of hepatic injury when either drug is administered to humans.

Summary. Exposure of rabbit liver slices to chlorpromazine in concentrations of 10^{-3} *M*, led to appreciable leakage of GOT and GPT into the surrounding medium. Promazine, in equal concentrations did not lead to an identifiable degree of leakage of these enzymes into the medium. The different effect of the two drugs on this system parallels what is known about their potential hepatotoxic effect in humans.

1. Zimmerman, H. J., Ann. N. Y. Acad. Sci. **104**, 954 (1963).
2. Devore, J. K., Daugherty, C., and Schneider, E. M., Gastroenterology **31**, 391 (1956).
3. Dickes, R., Schinker, V., and Deutsch, L., New Engl. J. Med. **256**, 1 (1957).
4. Bartholomew, L. G., Cain, J. G., Frazier, S. H., Peterson, M. G., Faulk, W. T., Soule, E. H., Fleisher, G. A., and Owen, C. A., Gastroenterology **34**, 1096 (1958).
5. Zimmerman, H. J. and Mao, R., Am. J. Med. Sci. **250**, 688 (1965).
6. Karmen, A., J. Clin. Invest. **34**, 131 (1955).
7. Wroblewski, F. and LaDue, J. S., Proc. Soc. Exptl. Biol. Med. **91**, 569 (1956).
8. Chien Li Huang and Kurland, A. L., Arch. Gen. Psychiat. **5**(5), 509 (1961).
9. Kok, K., Acta Physiol. Pharmacol., Neerl. **4**(3), 388 (1955).
10. Korn, R. J., Rock, W., and Zimmerman, H. J., Am. J. Med. Sci. **253**, 431 (1958).

Received Jan. 11, 1968. P.S.E.B.M., 1968, Vol. 128.

^{137}Cesium Retention in Mice of Different Ages* (33067)

CHARLES E. MILLER, ASHER J. FINKEL, AND NANCY B. WRIGHT
Argonne National Laboratory, Argonne, Illinois

The biological half-time for retention of ^{137}Cs in man has been of considerable interest. In a recent review, some investigators reported half-times as short as 10 days for newborn humans, 30–40 days for children, and 60–150 days for adults (1). We examined the retention of ^{137}Cs in mice as a function of age in order to have consistently acquired data for one mammalian species.

* Work performed under the auspices of the U. S. Atomic Energy Commission.

Methods. The ^{137}Cs chloride was injected intravenously into female mice of varying ages: 21 and 30 days; 3, 11, 22, and 32 months. Each injection of 0.1 ml contained about 0.2 μC carrier-free ^{137}Cs, which gave about 50,000 cpm in the mouse with our counting system. There were six mice in each age group except for the oldest group, which consisted of five mice. Each mouse was placed in a thin, perforated holder and counted under the face of an 8-inch diameter

TABLE I. ^{137}Cs Retention by Mice as a Function of Age.

Age of mice at injection (%):	Days required to decrease to percentage of injected dose					
	50	25	10	1.0	0.5	0.1
21 days	1.6	3.9	7.4	19.3	24.2	35.4
30 days	2.3	5.1	9.7	24.8	29.9	43.6
3 months	3.0	6.2	13.4	32.6	38.6	54.7
11 months	2.9	7.2	14.3	35.8	42.9	64.7
22 months	4.7	9.4	17.2	38.3	45.0	60.8
32 months	4.7	9.6	16.3	37.1	43.3	60.1

by 4-inch-thick NaI(Tl) crystal located in the human whole-body counter.

The ^{137}Cs content of each mouse was measured 2 min after injection and again about 400 min later. Subsequent measurements were made every day for the next 15 days and then less frequently until the ^{137}Cs content had decreased to 0.1% of the amount injected, a level that was reached between days 35 and 65.

Results and Discussion. The results obtained for the six age groups form a rather consistent pattern. In general, the younger the mice, the more rapidly they lost cesium (Table I). When the mice were 1 year of age or older, the retention values tended to cluster together, although the very old mice lost cesium somewhat more readily than did the other mature mice.

On the basis of these results with mice, if cesium metabolism can be extrapolated from mice to man, studies on very young humans will be expected to yield much shorter biological half-times for cesium retention than would be shown by young or old adults, a situation that has in fact been reported recently by Lloyd *et al.* (2).

Since another purpose of this study was to determine quantitatively the dependence of the biological half-time of ^{137}Cs in mice upon the age of the animal at the time of injection, the data obtained for each age group were subjected to extensive curve-fitting. This curve-fitting was performed with an electronic computer and the Variable Metric Minimization program (3), which successively alters the parameters to minimize an error function between the actual and computed values. The computed values were based on various sums of exponential terms and/or on various discontinuous straight-line segments on a semilog grid.

This computer analysis demonstrated that the retention data for ^{137}Cs injected intravenously into mice of various ages cannot be fitted with the sum of the same number of exponential terms by permitting only the parameters to vary. The detailed data and an extended discussion of the curve-fitting problems for each age group of mice are given in an Argonne National Laboratory report (4).

The best fitting combinations varied with the age of the mice at the time of injection and can be summarized as follows (parameters in Table II): The retention of injected cesium in very young mice (21 days old at time of injection) can best be expressed as the sum of three exponential terms for the first 38 days or until the ^{137}Cs content has decreased to less than 0.1% of the amount injected. Retention of cesium here is given by

$$R_{(0\rightarrow 38\,d)} = 0.277\ e^{-(0.693/731)t} + 0.619\ e^{-(0.693/3090)t} + 0.119\ e^{-(0.693/7423)t}.$$

Cesium retention for the 30-day-old mice follows the sum of three exponential terms for the first 31 days or until the ^{137}Cs content has decreased to 0.4% of the amount injected:

$$R_{(0\rightarrow 31\,d)} = 0.513\ e^{-(0.693/2072)t} + 0.371\ e^{-(0.693/4194)t} + 0.131\ e^{-(0.693/8614)t}.$$

For the next 14 days, the retention seems to follow a slightly longer single exponential term that has a half-time of 8680 days.

The retention in both the 3-month and 11-month-old mice from 2 min until 14 and 11 days, respectively, after injection could best be described as the sum of two exponen-

TABLE II. Parameters of the Best-Fitting Exponential Functions for Mouse Cesium Retention Curves.[a]

Age at injection	Time span (days)	No. of measurements	a_1	T_1	a_2	T_2	a_3	T_3
21 days	0–38	29	.277	731	.619	3090	.119	7423
30 days	0–31	25	.513	2072	.371	4194	.131	8614
	31–45	4	.151	8680				
3 months	0–14	17	.423	2166	.591	7412		
	16–35	9	.440	8610				
	46–60	4	.157	10818				
11 months	0–11	18	.521	2341	.492	9098		
	13–36	15	.464	9313				
	39–50	4	.314	10360				
	56–64	3	.191	22367				
22 months	0– 9	11	.999	6806				
	10–25	12	.775	8412				
	28–59	9	.498	9789				
32 months	0–14	17	.987	6908				
	16–45	13	.621	8937				
	45–59	4	.248	10883				

[a] Abbrev.: a_n = zero-time intercept of nth exponential term; T_n = half-time in minutes for nth exponential term.

tial terms (Table II). When plotted on a semilog grid, retention after these time periods follows a series of two straight-line segments for the 3-month-old mice and three straight-line segments for the 11-month-old mice. The retention curve for the 11-month-old mice demonstrates the largest number of distinct changes of slope. These discontinuous semilog straight-line segments provide a much better fit to the observed data than any combination of sums of exponential terms.

Cesium retention data for the 22-month and 32-month-old mice do not demonstrate an early curvilinear section on a semilog grid but both sets of points follow three distinct, discontinuous single exponential terms. The half-times of the three terms found for the 22-month-old mice are not greatly different from those found for the 32-month-old mice but the coefficients are considerably different (Table II). The older, 32-month-old mice follow the earliest half-time term for a longer time span and thus effectively lose the ^{137}Cs somewhat faster than do mice given intravenous cesium at 22 months of age.

The observation that the retention does not follow the sums of a series of exponentials but rather a series of single terms whose biological half-times vary with time and age is not incomprehensible. The sum of a series of terms would be associated with a multicompartmental model whereas ^{137}Cs is deposited mainly in the soft tissue that could be represented by a one-compartment model in which the retention is time (i.e., age) dependent. Furthermore, the fraction of a single dose deposited on a long-term basis (for example, in the skeleton) is evidently very small.

Summary. Analysis of the retention data of mice of various ages demonstrated that after intravenous injection the retention of ^{137}Cs chloride varied as a function both of the age of the animal at the time of injection and of the time since injection. The effective retention of cesium was lowest in the youngest mice, progressively higher for the older mice and then somewhat lower again for very old mice. Moreover, the retention does not change in a uniform manner that can be described by the sum of a series of exponential terms. If the retention is to be described accurately, it is frequently necessary to use a series of discontinuous exponential terms,

each of which describes the retention over a limited time span.

1. Intern. At. Energy Agency Symp. "Assessment of Radioactivity in Man," Vols. 1 and 2. Vienna, 1964.

2. Lloyd, R. D., Zundel, W. S., Mays, C. W., Wagner, W. W., and Pendleton, R. C., Radiation Res. **27**, 548 (1966).

3. Davidon, W. C., "Variable Metric Method for Minimization," ANL-5990 Rev. Argonne National Laboratory, 1959.

4. "Gamma-Ray Spectroscopy Group Annual Report," p. 103, ANL-7217. Argonne National Laboratory, 1965.

Received Jan. 15, 1968. P.S.E.B.M., 1968, Vol. 128.

Suppression of Cellular Proliferation in Weanling Rat Kidneys by Short-Term Fasting* (33068)

THEODORE L. PHILLIPS[1] AND LOUIS W. WACHTEL[2] (Introduced by Harvey M. Patt)

United States Naval Radiological Defense Laboratory, San Francisco, California; and Laboratory of Radiobiology, University of California Medical Center, San Francisco, California 94122

Investigations performed in weanling and adult male rats disclosed that labeling with tritiated thymidine (TdR-^{3}H) and mitotic activity are observable in the normal kidney at all ages. The response to unilateral nephrectomy in weanling male rats is manifested by a transient sixfold increase in the labeling index (1). Other investigations (2) demonstrated that mitotic counts in the kidneys of female weanling rats were elevated markedly at 48 and 72 hours after unilateral nephrectomy. When food was withheld for 1, 2, or 4 days, mitotic activity was dramatically reduced in these animals. Similar depression following starvation was noted in mice by Reiter (3) and in rats by Williams (4). This reduction in proliferative activity occurred in the remaining kidneys of nephrectomized rats as well as in the kidneys of starved control rats. These results and those previously reported in association with radiation effects (5–7) suggested that decreased food intake may be a contributing factor in the decreased cell turnover in the kidney after total body irradiation.

The present investigation was designed to study the effects of starvation at frequent time intervals following its initiation in both intact and unilaterally nephrectomized animals. It was hoped that such a study would shed light on the possible control mechanism regulating renal cell proliferation.

Materials and Methods. Animals. Female Sprague-Dawley rats, approximately 30 days of age, weighing an average of 100 gm were used. All animals were kept in cages on wire mesh to prevent access to stool or urine when starved; however, access to water *ad libitum* was assured.

Surgical procedures. Nephrectomies were performed through an incision in the left flank. The kidney was stripped of its capsule and all extraneous tissue, weighed, and prepared for autoradiography. Autoradiographic studies were also made with bone marrow obtained from the femur in order to determine whether the starvation effects were nonspecific.

Autoradiography. Labeling of cells engaged in DNA synthesis was accomplished by intravenous injection of 0.5 μC/gm body weight TdR-^{3}H (specific activity = 1.9 C/mmole). Animals were killed 45 min after TdR-^{3}H injection. Kidney material was prepared for autoradiography as previously

* This research was supported by the United States Naval Radiological Defense Laboratory and, in part, by the United States Atomic Energy Commission. Opinions contained herein are those of the authors and not to be construed as official views of the Department of Defense.

[1] Present address: Department of Radiology, U. C. Medical Center, San Francisco, Calif.

[2] Commander; Medical Service Corps, Present address: U. S. Naval Dental School, Bethesda, Maryland.