deoxyriboside, but synthesis starts immediately after addition of thymidine and proceeds stepwise. Three to four steps, followed by a long cessation of synthesis immediately prior to the first synchronous division, have appeared in all repetitions of this experiment. Deoxyribonucleic acid increases four- to eightfold before the first division. This is in line with the results of Jeener and Jeener (*5*), who demonstrated, by staining this mutant under conditions of deoxyriboside starvation and reactivation, that the cells can have many more than the normal two nuclei before they begin dividing. The fact that DNA more than doubles before division probably means, then, that the number of nuclei per cell more than doubles. On this basis the steps in the DNA curve may represent nuclear divisions. The appearance of cell division is correlated not with the amount of DNA multiplication, which is variable, but with the temporary cessation of DNA synthesis.

Well before the first division and at about the time of appearance of the DNA plateau, the rate of cell mass synthesis, as measured by turbidity, abruptly triples or quadruples and continues at the new rate through the first division cycle. Cell mass is synthesized linearly with time, rather than exponentially, throughout both the starvation and the reactivation phases. It is evident that the linear rate and the abrupt shift from one rate to another are similar to the results of mass measurements of single *Schizosaccharomyces* cells (*10*) if it is kept in mind that division may begin well before the daughter cells separate to form two viable units. It is tempting to assume that the simultaneous cessation of DNA synthesis and increase in the rate of protein synthesis are coordinated and decisive events in the sequence leading to cell division.

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Cholecystokinin Activity of Urine

Abstract. In the urine of men and animals was found a factor which evokes the contraction of the gall bladder. This factor increases in the urine after the application of a secretogenous stimulus to the duodenum and decreases after resection of the duodenum. A urine concentrate was prepared which has an effect similar to that of cholecystokinin administered intravenously and which was therefore called urocholecystokinin.

Ivy and Oldberg (*1*) reported the isolation of cholecystokinin from the duodenal mucosa. Intravenous administration of this hormone leads to contraction of the gall bladder without alteration of the blood pressure.

In assays on dog gall bladder *in situ* (*2*) and on guinea pig gall bladder *in situ* (*3*) I found that human urine injected intravenously also caused contraction of the gall bladder. Urine from a healthy fasting person evoked less contraction of the gall bladder than the same amount of urine from the same person after a fat-containing meal (Tables 1 and 2). Vagotomy of the experimental animal did not alter these results.

One milliliter of urine from duodenectomized guinea pigs caused less contraction of the gall bladder in the assay on guinea pigs than 1 ml of urine from normal control guinea pigs (Table 2). One milliliter of urine from guinea pigs given 1 ml of 0.1*N* HCl in the duodenum caused a greater contraction of the gall bladder than 1 ml of the urine from control guinea pigs.

The urine factor which evokes the contraction of the gall bladder can be adsorbed on benzoic acid (*4*). This method was modified in the following way: To 10 lit. of urine was added, drop by drop, 1.5 lit. of saturated ethanolic solution of benzoic acid. The precipitate formed was filtered off, and 1.5 lit. of acetone was added in order to dissolve the benzoic acid that was present. After further purification the precipitate was dried and pulverized. The dry powder was dissolved in physiological saline solution, at *p*H 3, and was administered intravenously.

The concentrates eluted from the benzoic acid did not alter the blood pressure. The urine factor causing the gall bladder contraction is thermolabile and does not stimulate duodenal motility.

These experiments show that there is evidence of a relation between cholecystokinin, Sandblom's blood factor (*5*), and the urine factor that evokes contrac-

Table 1. Assay on dog gall bladder *in situ*.

Material	Quantity	Intragall-bladder pressure level* (cm)	Standard error of the mean	No. of tests
Human urine from fasting persons	10 ml	0.7	± 1.6	15
Human urine from persons 2 hr after drinking 50 ml of olive oil	10 ml	1.1	± 0.25	6
Urocholecystokinin (benzoic acid adsorbate from human urine)	50 mg	0.8	± 0.18	14
Urocholecystokinin (benzoic acid adsorbate from human urine)	100 mg	1.5	± 0.17	14

* Water manometer.

Table 2. Assay on guinea pig gall bladder *in situ*.

Material	Quantity	Intragall-bladder pressure level* (cm)	Standard error of the mean	No. of tests
Human urine from fasting persons	1 ml	1.8	± 0.3	40
Human urine from persons 2 hr after drinking 50 ml of olive oil	1 ml	3.0	± 0.27	10
Urine from normal guinea pig	1 ml	4.2	± 0.32	12
Urine from duodenectomized guinea pig	1 ml	3.5	± 0.38	7
Urine from guinea pig given 1 ml of 0.1*N* HCl in the duodenum	1 ml	5.4	± 0.35	8
Urocholecystokinin (benzoic acid adsorbate from human urine)	5 mg	3.4	± 0.26	10
Urocholecystokinin (benzoic acid adsorbate from human urine)	10 mg	6.5	± 0.28	10

* Elevation of the gall in the pipette.

tion of the gall bladder. In the experiments in which the duodenum is stimulated to secrete more cholecystokinin through the administration of hydrochloric acid, the concentration of the gall-bladder–contracting factor in the urine is higher. If the chief source of cholecystokinin is excluded by duodenectomy, the concentration of the gall-bladder-contracting factor in the urine is lower.

Greengard *et al.* (*6*) showed that the blood serum inactivates cholecystokinin. As more than 120 minutes are necessary for total inactivation, it is possible that cholecystokinin reaches the kidneys in an active form.

The term *urocholecystokinin* is suggested for the factor, present in urine, which causes contraction of the gall bladder without altering the blood pressure and duodenal motility.

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25 July 1958

Metabolic Dissociation of Short-Lived Barium-137m from Its Cesium-137 Parent

Abstract. At 4 to 7 days after Cs^{137} administration, Ba^{137m} was found to exceed Cs^{137}-Ba^{137m} equilibrium proportions in bone and plasma by factors of 3 and 14, respectively, in the living animal. This demonstrated the in vivo escape of Ba^{137m} from sites of Cs^{137} accumulation. Liver tissue was slightly deficient in Ba^{137m}, whereas tissues such as bone marrow and spleen showed little or no deviation from equilibrium.

Cesium-137 is one of the more important potential hazards of fallout. Although the metabolism of radiocesium in biological systems has been studied in appreciable detail (*1*), no consideration has been given to the consequences of the differential behavior of Ba^{137m}, the radioactive daughter of Cs^{137}. The decay scheme is as follows:

$$Cs^{137} \xrightarrow[T\frac{1}{2} = 33\ \text{yr}]{0.52\text{-Mev } \beta} Ba^{137m} \xrightarrow[T\frac{1}{2} = 2.6\ \text{min}]{0.66\text{-Mev } \gamma} Ba^{137}$$

Cesium-137 decays by beta emission with a 33-year half-life to Ba^{137m} which in turn decays by gamma emission with a half-life of 2.6 minutes to a stable state.

In the organism, Cs^{137} would be expected to have a metabolic behavior similar to that of potassium, as both are alkali metals; Ba^{137m}, however, would be expected to behave more like the other alkaline earths, calcium and strontium (*2*). The metabolic dissociation of Ba^{137m} from the parent Cs^{137} has probably been overlooked experimentally because tissues are usually not measured within minutes after removal from the organism; this delay permits the reestablishment of equilibrium conditions in the tissue samples (the rate of establishment of equilibrium is governed by the half-life of the daughter, 2.6 minutes).

In the work reported here (*3*), the observations were made within minutes after removal of tissues; this permitted an estimation of the differential behavior of parent and daughter and an evaluation of the concentrations of the isotopes as they exist in the living animal.

Twelve normal albino rats of body weight about 150 g were injected intraperitoneally with about 60 μc of Cs^{137}-Ba^{137m}. At 4 to 7 days, the rats were anesthetized with sodium pentobarbital, and samples of blood, bone, and liver were removed from the living animal for radioassay. For each sample, an accurate time record was kept, starting at the time of removal from the body. The whole blood and liver were placed directly in test tubes, and radioactivity measurements were started within 1 to 2 minutes after removal. The femur diaphysis was used for the bone sample and was cleaned of extraneous tissue and marrow as rapidly as possible; measurements were usually started about 2 minutes after removal. Three blood samples were drawn into hematocrit capillaries, centrifuged, and the plasma and red blood cells separated so that radioassay was started on each fraction about 4 minutes after removal of blood from the animal. The samples were all counted in the usual well-type scintillation detector. In order to follow the expected decay or growth, a count-rate meter was employed with a recorder to give continuous reading of the counting rate over the 10 to 20 minutes required for attainment of equilibrium. Tissue weights were obtained after completion of the radioactivity measurements. The values given for liver and blood represent an average of tissues from four animals and, for bone, an average of tissues from eight animals. The results are expressed as follows: A, observed counts per minute per milligram of tissue; A_{eq}, counts per minute per milligram of tissue at equilibrium.

The observed radioactivities (A) in the various tissue samples as a function of time after removal from the body are presented as a semilog plot in Fig. 1. It is immediately apparent that the gamma activity in bone and blood decreased markedly with time to an equilibrium value, whereas that in liver increased slightly. Graphic analysis of these curves indicated that they represented two exponential rate processes: there was a short-lived component and a component of long enough half-life that decay could be neglected over this time scale. The short half-life was calculated in the usual way by plotting A–A_{eq} (irrespective of sign) versus time on a semilog scale (Fig. 1). As expected, a half-life of about 2.5 minutes for blood, bone, and liver was obtained; this is in agreement with that reported for Ba^{137m}.

The observations on plasma and erythrocytes are presented in Fig. 2. For convenience, the values are expressed in terms of A/A_{eq}. It is obvious that there was no appreciable change in the radioactivity of the red blood cells during the 20-minute counting period; the possible slight decline at the early time periods may have been caused by trapped plasma. The radioactivity in the plasma, however, decreased significantly with time, with a half-life of about 2.7 minutes.

There is little question that the Ba^{137m}

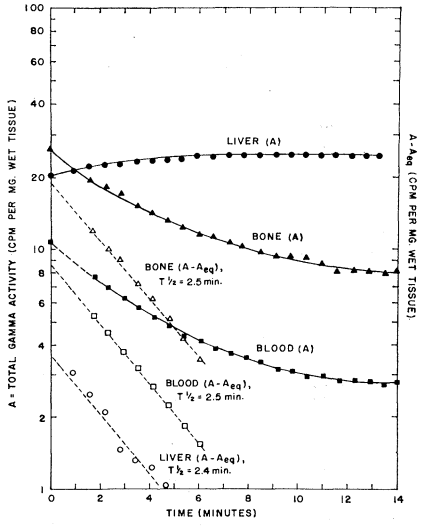

Fig. 1. Change in the total gamma activity (A) in liver, bone, and blood after removal from rats previously injected with Cs^{137}-Ba^{137m}, and the plot of their corresponding short-lived component ($A - A_{eq}$) with calculated halftimes ($T\frac{1}{2}$) given.

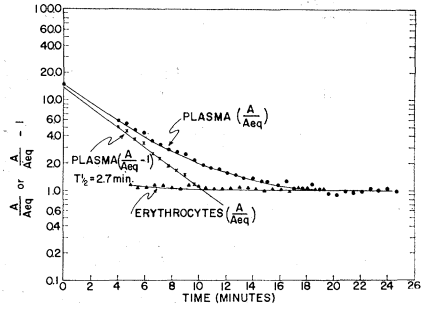

Fig. 2. Partition of excess Ba^{137m} between plasma and erythrocytes in the rat (see text for definition of terms).