In Vivo Experiment on the Metabolism of Cesium in Human Blood with Reference to Rubidium and Potassium

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ABSTRACT

Two single doses of coupled radioisotopes of $^{137}$Cs-$^{86}$Rb and $^{132}$Cs-$^{42}$K were orally administered to a human subject. Body retention, urinary and fecal excretions as well as the plasma and erythrocytes contents of radioisotopes were determined. The proportion of urinary to fecal excretion was found different in cesium and rubidium, the urinary excretion being 85.3% of the total in the former and only 68.1% in the latter. Loss of cesium in the sweat amounted to 1.5 and 3.5% of the total excretion for the first two days. Uptake by the plasma of oral dose was rapid and the whole blood content reached max. 11.4% of the dose of cesium at 1 hour, while 2.9 and 2.4% respectively of rubidium and potassium was reached. The levels in the erythrocytes seemed to grow at a slower rate in cesium than in the other alkali elements. The different feature of blood metabolism found in the alkali elements was interpreted by the slow rate of clearance of ingested cesium from blood. Daily fluctuations of fall-out $^{137}$Cs in blood and the errors involved in the assessment of the total body burden of $^{137}$Cs by blood analysis were also discussed.

INTRODUCTION

The analysis of blood was proposed as a promising aid for assessing the total
body burden of $^{137}\text{Cs}$. It has been generally realized that transition of cesium from the gastro-intestinal tracts to blood stream is complete and rapid, and therefore, the level of cesium in blood is likely to be very sensitive to dietary fluctuation of daily intake. However, a fraction of the total cesium in blood is considered to be in an equilibrium with that in the total body and only the remainder is sensitive to current intake. The extent to which blood concentration of $^{137}\text{Cs}$ is governed by current intake should justifiably be determined by metabolic pattern following the gastro-intestinal absorption.

The different distribution of cesium found by Yamagata and Iwashima comparing with rubidium and potassium also inspired to make a dynamic study *in vivo* on the metabolism of these elements in blood.

There seems a scanty evidence in literature of rapid transition rate of cesium in the human blood based on *in vivo* experiment. This must be partly because such an experiment requires quite a large dose of radioisotopes of cesium and makes administration of $^{137}\text{Cs}$ or $^{134}\text{Cs}$ to a healthy man practically impossible. However, a radioisotope of short half-life $^{132}\text{Cs}$ has become readily available in these years and this in couple with a scintillation detector of sufficiently high sensitivity made the present study possible.

In this study, particular emphasis was placed on the blood metabolism of cesium. Brief description was also made on the distribution and turnover in the body as well as on the blood metabolism of potassium and rubidium, but details are left for further examination and to be published elsewhere.

**METHODS**

*Radioisotopes*: Every radioisotope was supplied from Japan Atomic Energy Research Institute in Tokai. Radiochemical purity was proved satisfactory for the purpose of this experiment and the specific activity was as follows at the moment of administration. $^{42}\text{K}$ (half-life 12.5 h) 1.37 mCi/g, $^{86}\text{Rb}$ (half-life 18.6 d) 1.8 Ci/g and $^{132}\text{Cs}$ (half-life 6.55 d) 5.4 mCi/g.

*Measurements*: In Exp. 1, the body retention was periodically measured after administration by the use of a whole-body counter with a 20 cm×10 cm NaI (TI) crystal detector installed at National Institute of Radiological Sciences, Chiba. Excreta and blood samples were also measured on top of this detector. In Exp. 2, whole-body counting was abandoned and every excreta was measured on top of a 10 cm×10 cm NaI (TI) crystal detector housed inside a 10 cm lead shield. Blood sample in a plastic tube was placed inside a well cored in the same crystal detector and measured. In any case, energy resolution was made by employing a multi-channel pulse-height analyzer and γ-rays from couples of radioisotopes, namely, $^{134}\text{Cs}$ (0.67)–$^{86}\text{Rb}$ (1.08) and $^{134}\text{Cs}$ (0.67)–$^{42}\text{K}$ (1.51 MeV) were separately measured.

*Blood*: Samples of blood were withdrawn at frequent intervals on the day of administration and periodically thereafter. Blood (5 ml) was collected in heparinized tubes and after adequate mixing immediately centrifuged at 3000 rpm for 10 minutes.
Each fraction of the plasma and erythrocytes was respectively made up to 5 ml in volume by adding normal saline solution and measured of radioactivity.

**Excreta:** An aliquot of 24 hours urine and untreated but homogenized 24 hours feces were measured.

**Perspiration:** On the beginning two days after administration, the underwears made of double antiseptic gauze were put on by the subject. Every 24 hours the underwears were taken off and impregnated with water and with these the body was rubbed to remove secretion on the skin. Gauze was pressed into a plastic container to make a definite volume for activity measurement.

**EXPERIMENT**

**Experiment 1:** In consideration of possible disturbance by increasing the background activity resulted from 1.08 Mev $^{86}$Rb in the region of 0.67 Mev $^{132}$Cs, the former radioisotope was administered two days in advance of $^{132}$Cs administration. 9.43 µCi of $^{86}$Rb in the form of RbCl was orally administered to a healthy man NY (45 years of age and 54.5 kg body weight) at 1100 on the 2nd of March 1965. The amount of stable rubidium in this dose was calculated to be 5.2 µg. At 1200 on the 4th of March, about 30 µc of $^{132}$Cs in the form of CsCl was orally administered to the same subject.

**Experiment 2:** This experiment was conducted on the same subject (NY) about six months after Exp. 1 by use of a coupled radioisotopes $^{42}$K-$^{132}$Cs. Prior to the experiment, the absence of residual activity in the body from $^{86}$Rb was confirmed by wholebody counting. On the same day, the plasma and blood volumes of the subject were determined by a conventional method by intravenous injection of a 10 yCi dose of albuminoid-$^{131}$I and found to be 2301 and 3232 ml respectively. The hematocrit was found to be 49%.

About a month was required to eliminate $^{131}$I activity in the blood which might interfere with the experiment. At 1000 on the 7th of October, 174 µCi of $^{42}$K and 33.3 µCi of $^{132}$Cs in the form of chlorides in 0.02% sodium chloride solution were orally administered to the subject. The amounts of the stable potassium and cesium were calculated to be 127 and 6.2 mg, respectively. Complete sampling of urine and feces was continued for the period of two weeks to obtain the body retention by subtraction of the total excretion from the applied dose. Blood sampling had been continued at variable intervals up to the 25th day.

**RESULTS AND DISCUSSION**

**Retention:** The amount of $^{132}$Cs remaining in the body in Exp. 2 was calculated by subtracting the sum of urinary and fecal excretions from the applied dose. The results are plotted in Fig. 1 for the period of two weeks after administration. The curve can be fitted to a two-component exponential equation, about 10.7% fraction being excreted with a half-time of 0.88 day and the remaining 89.3% with a long-term biological half-time of 60 days.
In Exp. 1, the body retention was followed by whole-body counter up to 55 days and a long-term half-time of 71.5 days was obtained for $^{132}$Cs while a value of 50.4 days was obtained for $^{86}$Rb by 120 days measurements.

Inuma et al.\cite{inuma1970} reported long-term half-times for 3 male Japanese ranging from 65.5 to 82.0 days by $^{132}$Cs single dose experiments and Yamagata\cite{yamagata1970} reported a value of 76 days by the analysis of stable cesium in the diet and human tissues. There seems a real difference for people living in various regions of the world, because the data from Germany, the United States and Canada are concentrated in the range 100~140 days\cite{yamagata1970}.

**Excretion**: During the first 24 hrs after administration, the elimination of cesium from the body mainly follows the urinary route and results in high urine levels. This is common in three radioisotopes studied but the largest fraction was found in cesium, 4.82 and 6.66% of dose respectively in Exp. 1 and 2, and about a half was found in rubidium and potassium (Table 1). Excretion of potassium could not be followed after the 3rd day because of its short half-life, but rather high urine levels were maintained in the 2nd and 3rd 24 hrs following the 1st. The pattern is quite in contrast to that of rubidium and cesium which showed a large decrease in the excretion rate in the first few days. These patterns can be clearly realized by taking the ratios for pairs of radioisotopes as shown in Table 1.

Fecal excretions were followed for one and two weeks respectively in Exps. 1 and 2. The results are shown in Table 2. For the first week after administration, a daily fecal excretion of 0.38% (Exp. 2) and for the first 5 days 0.41% (Exp. 1) of administered dose were observed. For the second week, the fecal excretion rate decreased to one-third (Exp. 2), showing 0.12%/d. The results are in the ranges studied by others, namely, 0.20 to 0.44% for the first week and 0.09 to 0.14% for the second\cite{yamagata1970}.
IN VIVO EXPERIMENT ON THE METABOLISM OF CESIUM IN HUMAN BLOOD

Table 1. Urinary excretion of $^{42}$K, $^{86}$Rb and $^{132}$Cs in the first five days after a single ingestion
(Per cent of administered dose)

<table>
<thead>
<tr>
<th>Time of collection after ingestion</th>
<th>$^{132}$Cs</th>
<th>$^{86}$Rb</th>
<th>$^{42}$K</th>
<th>Rations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp. 1</td>
<td>Exp. 2</td>
<td>Exp. 1</td>
<td>Exp. 2</td>
</tr>
<tr>
<td>5.5 hr</td>
<td>3.53</td>
<td></td>
<td>1.71</td>
<td>0.49</td>
</tr>
<tr>
<td>8.3</td>
<td>1.25</td>
<td></td>
<td>0.62</td>
<td>0.50</td>
</tr>
<tr>
<td>11.5</td>
<td>0.53</td>
<td></td>
<td>0.37</td>
<td>0.70</td>
</tr>
<tr>
<td>21.0</td>
<td>1.35</td>
<td></td>
<td>0.93</td>
<td>0.69</td>
</tr>
<tr>
<td>1st 24 hrs</td>
<td>4.82</td>
<td>6.66</td>
<td>2.20</td>
<td>3.63</td>
</tr>
<tr>
<td>2nd</td>
<td>1.68</td>
<td>2.50</td>
<td>0.94</td>
<td>3.03</td>
</tr>
<tr>
<td>3rd</td>
<td>1.85</td>
<td>1.27</td>
<td>1.03</td>
<td>2.08</td>
</tr>
<tr>
<td>4th</td>
<td>1.03</td>
<td>1.38</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>0.88</td>
<td>1.12</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Total of 5 days</td>
<td>10.26</td>
<td>12.93</td>
<td>5.67</td>
<td>&gt; 8.74</td>
</tr>
</tbody>
</table>

* $^{42}$K/$^{132}$Cs divided by $^{86}$Rb/$^{132}$Cs

Table 2. Fecal excretion of $^{42}$K, $^{86}$Rb and $^{132}$Cs after a single ingestion
(Per cent of administered dose)

<table>
<thead>
<tr>
<th>Tracer</th>
<th>$^{132}$Cs</th>
<th>$^{86}$Rb</th>
<th>$^{42}$K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. No.</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Day after ingestion</td>
<td>1</td>
<td>0.84</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.61</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.36</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.23</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.25</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-11</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

Rubidium or potassium especially is preferentially excreted through the fecal route in comparison with cesium. For the first three days, the fecal excretion rates were 0.68 and 0.98% /d respectively of $^{86}$Rb and $^{42}$K, while only 0.60 and 0.57% /d of $^{132}$Cs were excreted.

A striking observation in our results was the difference in the proportion of urinary excretion between cesium and potassium or rubidium (Table 3). For the period of two weeks after ingestion, 85.3% of cesium was excreted through the urinary route (Exp. 2). By this route, however, rubidium was excreted only 68.1% of the total for the period of a week. Potassium excretion was observed for only three days but the decreasing proportion of urinary excretion in the first few days (Table 3) may suggest a lower percentage of urinary excretion in a longer period of observation.

Fujita et al. determined the potassium and $^{137}$Cs contents in the diet and excreta in three or four persons and found the urinary excretion of 82% (range: 74~87%) in $^{137}$Cs and 80% (range: 78~81%) in potassium. Recent study by Linuma et al. by the use of $^{132}$Cs tracer also shows in four subjects 87.0% excretion ranging...
from 82.0 to 89.8%. Present observation is in the range reported for cesium in Japanese, but in contradiction with the higher values for potassium reported by Fujita et al and further inquiry is needed for the stable potassium distribution between feces and urine.

Loss in the sweat was determined for the first two days in Exp. 2. In the first 24 hrs, 0.11 and 0.12% of the administered dose respectively of $^{132}$Cs and $^{42}$K were excreted through perspiration; these amount to 1.5 and 2.7% respectively of the total $(U+F)$ excretion in the same period. In the second 24 hrs, the excretion was 0.10% in either radioisotope, amounting to 3.5 and 2.6% of the total excretion respectively of $^{132}$Cs and $^{42}$K.

It is of course extremely difficult to determine the excretion in sweat quantitatively and there seems only an information on this matter by Rundo9) who reported that only about 0.01% of the oral dose was excreted one day after ingestion. If the present results are correct, a correction for the loss in the sweat, amounting to a few per cent of the $(U+F)$ excretion, should be made when the body retention is calculated basing upon the excretion data.

**Blood Metabolism-General Feature:** The amount and distribution of $^{42}$K, $^{86}$Rb and $^{132}$Cs in the plasma and erythrocytes after an oral administration are shown in Fig. 2; errors involved in the activity measurement of $^{132}$Cs were larger in Exp. 1 than in Exp. 2, therefore only the result for $^{132}$Cs in the latter is shown.

Blood plasma obtained by centrifugation is free of cells but the cellular fraction contains an unknown amount of the plasma, so that if correction has not been made, the radioisotopes in the cells are liable to be overestimated in the earlier stages of transition when the levels of radioisotopes in the plasma are high comparing with those in the cells. On the other hand, washing of the centrifuged cellular fraction, that is usually performed, is likely to introduce a loss by leaching of radioisotopes associated with the cells and lead to an underestimation of the radioisotopes in the erythrocytes. In consideration of this and in view that correction for incomplete separation of blood fraction is possible basing upon data on the blood and plasma.

<table>
<thead>
<tr>
<th>Tracer</th>
<th>$^{132}$Cs</th>
<th>$^{86}$Rb</th>
<th>$^{42}$K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. No.</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Day after ingestion</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>88.8</td>
<td>84.3</td>
<td>70.5</td>
</tr>
<tr>
<td>2</td>
<td>80.4</td>
<td>77.4</td>
<td>63.1</td>
</tr>
<tr>
<td>3</td>
<td>77.9</td>
<td>85.3</td>
<td>64.8</td>
</tr>
<tr>
<td>4</td>
<td>85.7</td>
<td>83.7</td>
<td>65.5</td>
</tr>
<tr>
<td>5</td>
<td>81.8</td>
<td>87.1</td>
<td>66.7</td>
</tr>
<tr>
<td>6</td>
<td>87.2</td>
<td>83.5</td>
<td>74.2</td>
</tr>
<tr>
<td>7</td>
<td>81.9</td>
<td>(Total)</td>
<td>72.4</td>
</tr>
<tr>
<td>8</td>
<td>86.3</td>
<td>68.1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>89.7</td>
<td>(Total)</td>
<td></td>
</tr>
<tr>
<td>10–11</td>
<td>88.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>83.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>83.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>83.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85.3</td>
<td>(Total)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
volumes determined by the iodine method on the same subject (see under Exp. 2),
the condition of centrifugation was set up as described under methods and no
washing was made. Under this condition of centrifugation, the plasma:cell volume
ratio was found to be 45:55 on the average, while the usual separation method
(washing once with normal saline solution and recentrifuge at 4000 rpm for 30 min.)
resulted in ca 50:50 ratio.

From 20 min to 1 hr after oral administration, none of the radioisotopes was
detected in the erythrocytes. But in this same period, a large increase was observed
in the plasma amounting to 11.4% of the dose in $^{132}$Cs at 1 hr. Rubidium and
potassium also showed peak plasma levels at 1 hr, but the levels were much lower,
2.9 and 2.4% respectively.

In the second stage, from 1 hr to 24 hrs, $^{132}$Cs increased in the erythrocytes
and reached a peak value of 5.0% of the dose at 24 hrs, when the plasma had lost
90% of its content at 1 hr, the cell:plasma ratio being ca 4:1. The plasma levels
decreased at a faster rate than that at which the erythrocytes levels increased, so
that the whole blood content of $^{132}$Cs decreased since 1 hr. In contrast to rather
slow growing levels of $^{132}$Cs in the second stage, the levels of $^{42}$K and $^{86}$Rb seemed
to grow in the erythrocytes at a faster rate and reach a constant level earlier than
the $^{132}$Cs levels reach, especially in the case of $^{42}$K.

After 24 hrs the $^{132}$Cs levels continued to decrease in the plasma but seemed
to remain almost constant in the erythrocytes for a while. On the sixth day the
$^{132}$Cs level in the plasma fell down below the limit of detection, the cell:plasma
ratio being 10:1 or smaller, so that the whole blood content only was followed
thereafter up to the 25th day.

**Fig. 2.** Cellular and extracellular contents of $^{42}$K, $^{86}$Rb and $^{132}$Cs in blood after
a single ingestion
The time course of the whole blood $^{132}\text{Cs}$ content after 24 hrs is plotted in Fig. 3 on a semi-logarithmic scale. It shows the blood levels of $^{132}\text{Cs}$ decreased at a rate (half-time 12.5 d) faster than that at which the total body $^{132}\text{Cs}$ had eliminated (half-time 60 d). This suggests that no steady state had reached between the blood and body even at the 25th day of administration and at that time the blood still contained approximately 1.5% of the ingested dose or 2.2% of the body retention.

The results obtained for $^{132}\text{Cs}$ in the present study are in good agreement with reported findings by Rosoff et al.4) in general feature and with Madshus and Strømme10) in the later stages. The latter authors followed the elimination from the blood up to the 50th day of a single $^{137}\text{Cs}$ dose and reported two different rates of cesium elimination from the blood, one component having a half-time of ca 8 days and the other ca 40 days.

Interpretation of the Different Partition of Potassium, Rubidium and Cesium between the Plasma and Erythrocytes: Approximately 95% of potassium in human blood is located in the erythrocytes, and 98% of the stable rubidium was also found as previously reported5), while in this fraction of the blood, either of the stable cesium and the fall-out $^{137}\text{Cs}$ was found only 3/4 of the total. Love and Burch11) showed by an in vitro experiment that the eventual quantitative partition of the isotopes of potassium, rubidium and cesium was nearly the same between the erythrocytes and plasma after they were added to the plasma. In the present study in vivo it was confirmed that 1/10 or less of the blood $^{132}\text{Cs}$ was located in the plasma after 6 days of oral dose. Oral dose experiments conducted by Rosoff et al.5) and Madshus and Strømme10) also showed insignificant levels in the plasma in three cases several days after ingestion.

The contradiction between those two groups of observation seems to be due to the difference between single and chronic exposures to oral doses. The slow rate of clearance of ingested cesium from the plasma necessarily causes accumulation in blood when doses are given chronically. This is not the case in rubidium or potassium in which the rate of clearance is much faster.
Approximate estimation of the integrated levels of cesium in blood can be made for chronic daily exposures basing upon the following assumptions which were derived from the present observations: (1) the elimination in whole blood takes place exponentially with a single rate having a half-time of 12.5 days after one day, (2) the elimination in the plasma takes place with two rates, ca 3 day half-time between 1-6 day and 12.5 day half-time thereafter, (3) the levels in blood (per cent of daily dose in kilogram of whole blood) are 2 after one day in the whole blood, 0.4 and 0.13 in the plasma, respectively after one and 6 days, (4) contribution by the components having faster rates of elimination in the period 0-24 hrs after ingestion is estimated from Fig. 2 and (5) a constant daily dose.

The result of estimation indicates that approximately 37 and 6% of daily dose is to be found in kg of blood, respectively in the whole blood and plasma; these values are in good agreement with the observations for chronic exposure to the fall-out $^{137}$Cs described under daily fluctuation.

Mathematical Analysis of the Different Blood Metabolism in Cesium and Rubidium or Potassium: The blood metabolism, demonstrated in Fig. 2, can be analyzed mathematically by assuming a model. To set the equation, a simple scheme of the blood metabolism with three compartments have been assumed (Fig. 4). The rate constants, $\lambda_1$, $\lambda_2$ and $\lambda_3$ represent first-order reactions between the compartments, gastro-intestinal absorption, penetration or diffusion to body fluid and uptake by the erythrocytes, respectively. Then the time course of the plasma content of an element ($y$) which has been orally administered in a single dose ($q$) can be given by the equation:

$$y=qe^{-\lambda t} (1-e^{-\lambda_2 t})$$

where $\lambda = \lambda_2 + \lambda_3$. The shape of the curve for this function is very similar to those shown in Fig. 2 when $y$ is plotted against $t$ and pertinent values are taken for $\lambda$ and $\lambda_2$.

The curve has a maximum value of $y$, which can be obtained by solving $\frac{dy}{dt} = 0$. The solution is

$$y = qa(1 + \alpha) - \frac{(1 + \frac{1}{\alpha})}{\alpha}$$

where $\alpha = \frac{\lambda}{\lambda_1}$. The result indicates that the peak content of an element in the plasma is a function of the ratio of the rate constants $\lambda_1$ and $\lambda$ and the larger the ratio the

![Fig. 4. A simple scheme of the blood metabolism with three compartments](image)
higher the peak. Thus, the observed curves in Fig. 2 demonstrate that the difference
between the rates of gastro-intestinal absorption and clearance from the plasma is
much greater in cesium than in potassium or rubidium. In other words, the elimi-
nation of cesium from the plasma takes place much slower than the gastro-
intestinal absorption. It should be mentioned that Love and Burch found by an in
vitro experiment that the exchange rate of cesium between the plasma and blood
cells was less than one-fifth as great as potassium or rubidium.

Discussion on the mechanisms involved in the gastrointestinal absorption and
plasma clearance is beyond the scope of this article. It should be suggested,
however, that cesium is a member of the alkali metal elements having similar
properties such as ionic valency and potential, but the similarity is not complete
and the differences especially in ionic radius, permeability and adsorptive charac-
ter may result in different behavior in various phases of physiological processes.

Daily Fluctuation in Blood: A rapid transition of ingested cesium to the blood
stream may result in a daily fluctuation of the fall-out $^{137}$Cs in blood, so that the
size of fluctuation must be estimated to know possible errors caused by the time of
blood sampling in a day in the assessment of total body burden by the analysis of
blood.

Basing upon the observations obtained in a single dose experiment (Fig. 2), the
integrated levels of cesium in blood in a chronic exposure can be drawn. Fig. 5
was drawn by introducing the following assumptions: (1) three meals are taken at
0700, 1300 and 1900 every day and (2) each meal contains equal dose of cesium.
Absolute fluctuations thus estimated are shown in per cent of daily dose in Fig. 5.

![Graph showing daily fluctuation of Cs and Rb levels in blood](image)
The highest level of cesium in blood will be found around one hour after dinner and the lowest just before the breakfast, the maximum deviation in a day being 0.8 and 1.3% of the daily intake, respectively in the whole blood and plasma.

The fluctuations actually are superimposed on rather constant levels resulted from integration of the components having slower rates of elimination from blood. Contribution from these components has been roughly estimated in a preceding chapter basing upon a single dose experiment, but more practical information is available from the results of blood analysis for the fall-out $^{137}$Cs and the total body measurements.

In Table 4 are shown the results of measurements made on subject NY for the period June 1964 and January 1965. Daily intake ($q$) was estimated basing on the equation $Q = (T/2) q/0.693$ where $Q$ is the total body burden. The biological half-time ($T/2$) of cesium in subject NY was taken as 71.5 days which was derived in Exp. 1.

Supposing roughly 30% of daily intake is located in the whole blood, another observation (i.e., 1/4 of the cesium in the whole blood is localized in the plasma) would indicate that 7.5% on the average is to be found in the plasma. Then, the fluctuation in a day due to short-term components of elimination of currently ingested $^{137}$Cs relative to the total blood-$^{137}$Cs would be 2.7 and 17% at the highest respectively in the whole blood and plasma (Fig. 5).

A relative deviation of 2.7% at the highest in the whole blood seems insignificant in assessing the total body burden when the analysis of whole blood is based, so that at what time of a day the sample blood is to be withdrawn from a donor does not matter. On the other hand, if the plasma was chosen as a material on the basis of which the total body burden should be assessed, possible errors due to the time of blood sampling would become significantly large.

Considerably large variation, a relative standard deviation around the mean of about 15% found in the figures in the third column of Table 4, namely, the whole blood $^{137}$Cs levels must be attributable to sources other than the time of blood collection in a day.

Assessment of the Total Body Burden basing upon the Blood Levels of Cesium-137: Variable levels of blood-$^{137}$Cs in a subject observed during a period in which the total body burden and the estimated daily intake seemed rather constant (Table 4) suggest the presence of a day to day or meal to meal variation of dietary intake. This is very likely when a variety of foodstuffs and variable $^{137}$Cs levels are taken into consideration.

In order to estimate the size of fluctuation of $^{137}$Cs in the whole blood when the daily intake is variable, the relation between the total body and blood contents has been analyzed mathematically.

The total body burden $Q_w$ is given as the sum of fractional body burdens $q_1$ and $q_2$, respectively having a fast and a slow excretion rates. And when a constant daily intake is assumed, $Q_w$ can be expressed by the two exponential functions of
Table 4. Relation between daily intake and blood concentration of $^{137}$Cs as deduced from observed levels in total body and blood for subject NY (June 1964 - January 1965)

<table>
<thead>
<tr>
<th>Time</th>
<th>Total body $^{137}$Cs nCi (Q)</th>
<th>Whole blood $^{137}$Cs pCi/kg blood</th>
<th>Estimated* daily intake pCi/d (q)</th>
<th>Per cent of daily intake in kg of whole blood</th>
<th>Relation** factor body/blood $F_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>17.0</td>
<td>60.1</td>
<td>165</td>
<td>36.4</td>
<td>88</td>
</tr>
<tr>
<td>Aug.</td>
<td>17.8</td>
<td>53.3</td>
<td>173</td>
<td>30.8</td>
<td>103</td>
</tr>
<tr>
<td>Oct.</td>
<td>17.3</td>
<td>72.1</td>
<td>168</td>
<td>42.9</td>
<td>75</td>
</tr>
<tr>
<td>Nov.</td>
<td>18.7</td>
<td>59.5</td>
<td>181</td>
<td>32.8</td>
<td>97</td>
</tr>
<tr>
<td>Dec.</td>
<td>17.8</td>
<td>54.0</td>
<td>173</td>
<td>31.2</td>
<td>102</td>
</tr>
<tr>
<td>1965</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan.</td>
<td>17.6</td>
<td>45.5</td>
<td>171</td>
<td>26.6</td>
<td>119</td>
</tr>
<tr>
<td>Average for the period of observation</td>
<td>17.7</td>
<td>57.4</td>
<td>172</td>
<td>33.4</td>
<td>~100</td>
</tr>
<tr>
<td>Relative standard deviation of the mean (%)</td>
<td>3</td>
<td>16</td>
<td>3</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

* Based on the equation $Q = \frac{q T}{0.693}$ assuming $T$ as 71.5 days in subject NY.

** $F_0$ is the total body burden divided by the total blood content of $^{131}$Cs assuming the total blood volume as 3232 ml.

the time

$$Q_b=\frac{f_1 I}{k_1}(1-e^{-k_1 t})+\frac{f_2 I}{k_2}(1-e^{-k_2 t})$$

in which

$I$=daily intake of $^{137}$Cs  
$f_1$=fraction of the daily intake being excreted at the fast excretion rate  
$f_2$=fraction of the daily intake being excreted at the slow excretion rate  
$f_1+f_2=1$  
k_1=the fast biological fractional excretion rate  
k_2=the slow biological fractional excretion rate

Similar function is given for the total blood content, but in this case, at least three components are required to describe the observed elimination.  
$$Q_b=q_3+q_4+q_5$$

in which $Q_b$ is the total blood content and $q_3$, $q_4$ and $q_5$ are fractional blood contents.  
The total blood content in a constant chronic exposure can be expressed similarly by

$$Q_b=\frac{f_3 I}{k_3}(1-e^{-k_3 t})+\frac{f_4 I}{k_4}(1-e^{-k_4 t})+\frac{f_5 I}{k_5}(1-e^{-k_5 t})$$

in which $f_3+f_4+f_5=1$
f₃, f₄ and f₅ = fractions being eliminated at the fast, medium and slow rates, respectively,
k₃, k₄ and k₅ = the fast, medium and slow elimination rates respectively.

The slow elimination rate k₅ in the blood can be replaced by the slow excretion rate k₂ in the body when the fast components have been disappeared and an equilibrium state is reached between the body and blood. In such an equilibrium state, k₁ and k₃, having fast elimination rates of about one day and two hours, respectively (see Table 5) can be neglected for the first approximation. Then the total body burden Qₜ₀ and blood content Qₜ₀ are in a chronic equilibrium state can be expressed by

\[ Qₜ₀ = \frac{f₂ I}{k₂} \quad \text{and} \]
\[ Qₜ₀ = \left( \frac{f₄}{k₄} + \frac{f₅}{k₅} \right) I \]

**Table 5.** Numerical data for the biological elimination of cesium in the total body and blood

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Body</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>f₁ = 0.1</td>
<td>f₅ = 0.942</td>
</tr>
<tr>
<td>Medium</td>
<td>f₂ = 0.9</td>
<td>f₄ = 0.057</td>
</tr>
<tr>
<td>Slow</td>
<td></td>
<td>f₅ = 0.001</td>
</tr>
<tr>
<td>Fractional elimination rate (day⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>k₁ = 0.79</td>
<td>k₅ = ~7</td>
</tr>
<tr>
<td>Medium</td>
<td>k₂ = 0.0097</td>
<td>k₄ = 0.0554</td>
</tr>
<tr>
<td>Slow</td>
<td></td>
<td>k₅ = k₂ = 0.0097</td>
</tr>
<tr>
<td>Half-time (day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>T₁ = 0.88</td>
<td>T₅ = ~0.1</td>
</tr>
<tr>
<td>Medium</td>
<td>T₂ = 71.5</td>
<td>T₆ = 12.5</td>
</tr>
<tr>
<td>Slow</td>
<td></td>
<td>T₇ = T₈ = 71.5</td>
</tr>
<tr>
<td>Total body burden or blood content in a chronic equilibrium (1=daily intake)</td>
<td>Qₜ₀ = 92.8 l</td>
<td>Qₜ₀ = 1.13 l</td>
</tr>
<tr>
<td>Relation factor in a chronic equilibrium</td>
<td>Fₜ = 82</td>
<td></td>
</tr>
<tr>
<td>Relation factor in a single dose equilibrium</td>
<td>F' = 900</td>
<td></td>
</tr>
</tbody>
</table>

The relation factor \( Fₜ \) between the total body and blood contents in a chronic equilibrium state can be given by

\[ Fₜ = \frac{Qₜ₀}{Qₜ₀} = \frac{k₄ f₂}{k₅ f₅} \]

The factor \( Fₜ \) approximates to \( F' \) which is the relation factor in an equilibrium state after a single exposure if the medium elimination component in the blood was negligible comparing with the slow one.

\[ F' = \frac{f₂}{f₅} \]
Numerical data shown in Table 5 indicate that this is not the case in a chronic exposure to $^{137}$Cs.

Three models of incident are assumed of change in the daily intake of $^{137}$Cs in a chronic equilibrium state. In Model 1, a single extra dose $I'$ is assumed to be given at time 0. The change of the relation factor $F$ can be expressed as a function of time

$$F = \frac{Q_a - Q_b}{Q_b} = \frac{Q_{ba} + f_1 I e^{-k_1 t} + f_2 I' e^{-k_2 t}}{Q_{ba} + f_3 I e^{-k_3 t} + f_4 I' e^{-k_4 t} + f_5 I e^{-k_5 t}}$$

In Model 2, a step function change in the daily intake by a factor of $a$ is assumed; the daily intake changes from $I$ to $aI$ at time 0. A change in the fractional body burden or blood content $q$ is

$$\frac{dq}{dt} = aI - kq$$

in which $k$ is a fractional elimination rate. The solution is given by

$$q = Q e^{-kt} + aQ(1 - e^{-kt})$$

in which $Q$ is the fractional body burden or blood content at time 0 and $Q = \frac{I}{k}$.

In Model 3, a linear change in the daily intake is assumed; the daily intake changes from $I$ to $I'$ at time 0 and $I'$ is given by $I' = I + Jt$ in which $J$ is a proportionality factor. A change in the fractional body burden or blood content $q$ is

$$\frac{dq}{dt} = (I + Jt) - kq$$

The solution is given by

$$q = Q + Jt - \frac{J}{k} Q(1 - e^{-kt})$$

in which $Q$ is the fractional body burden or blood content at time 0 and $Q = \frac{I}{k}$.

The relation factor $F$ in Models 2 and 3 can be calculated by summing up the fractional body burdens and dividing by the summation of fractional blood contents by use of the general formulae shown above. Pertinent data for numerical calculation are shown in Table 5.

Possible Errors involved in the Assessment: Fig. 6 demonstrates the changes in the relation factor between the body and blood after changes have been made in the daily intake in a number of incidents, most of which is very likely to happen.

Examination of the diet at dormitories of a college$^{12}$ showed in September 1960 a maximum meal to meal variation of a factor of 5 and a day to day one of a factor of about two in a few days. A replica of this observation is demonstrated in Models Ia and Ib by assuming a single extra dose amounting to a twice or a ten-times the daily chronic intake. An year to year change of a factor of two in the daily intake of $^{137}$Cs has been frequently observed in these years and this is demonstrated in Models IIa and IIb for the first approximation by a step function change by a factor of two.
Fig. 6. Changes in the relation factor \( F \) between the body and blood after changes have been made in the daily intake \( I \) \( (F=F_0=1 \text{ at time } 0) \).

Observed levels of \(^{137}\text{Cs}\) in the standard diet and the average body burden of laboratory personnel at the Institute of Public Health are shown in Fig. 7 for the period January 1963 and October 1965. The diet samples were purchased in Tokyo at three months intervals. A rapid increase from October 1963 toward April 1964 in the diet levels is followed by an increase in the body burden from November 1963 toward June 1964 with a time lag of a few months. The rate of increase in the diet level is a factor of 2 in six months, while the rate in the body is about a factor of 1.6 in 7 months. This observation is faithfully imitated in Model 3.

In Fig. 6, changes in the factor \( F \) within a day are not shown, because the blood component having the fast elimination rate \( (T_k=ca. 0.1 \text{ day}) \) was omitted in the calculation. Only in Model 1, in which an incidental extra dose is assumed, changes in the factor \( F \) within a day exceed those would happen after one day.
A step function increase (or decrease) in the daily intake (Model 2) is followed by a decrease (or increase) in the $F$ value which reaches a minimum (or maximum) in about 20 days (or 40 days) and then gradually approaches to $F_0$.

A similar case is in a linear increase (Models 3a and 3c) but the $F$ value reaches a minimum much later than in a step function change and then approaches to $F_0$ (this is not shown in Fig. 6). In a linear decrease (Model 3b), a change in the $F$ value is discontinuous and after the time when the daily intake has decreased to 0, it approaches to $F_0$ gradually (this is not shown in Fig. 6).

In both cases of a step function and a linear changes, a maximum deviation of the $F$ value from $F_0$ is larger in a decrease in the daily intake than in an increase of identical size.

At all events, the maximum deviation of the relation factor under assumed conditions of change in the daily intake was found to be about 30%. Considerably large variation observed in the whole-blood $^{137}$Cs levels in an apparently equilibrium condition between the body and diet even in a same subject may be attributable to an incidental extra large or small dose in the dietary intake.

Conclusion: Estimation of possible errors involved in the assessment of total body burden of $^{137}$Cs in people by the analysis of blood has been made basing upon the results obtained by in vivo tracer experiments on the metabolism of cesium in the blood and body. The different rate of elimination of cesium in the body and blood results in variable ratios of the total body and blood contents when a change has been made in the daily intakes in an assumed constant chronic exposure. The variable daily intakes of the fall-out $^{137}$Cs that have been generally observed so far in Japan may cause the variation of the relation factor body : blood amounting up to about 30%.

When the fall-out rate increases and is followed by growing levels in the dietary intake, the relation factor will decrease and vice versa. Therefore, the mean value of the factor obtained in observations made on several persons during the period June-December 1964 may change in the range of $\pm$30% when the daily
intake is variable in the ranges described previously. The numerical data for the factor were previously reported as being 6 on the average if it is defined as follows:

\[ f = \frac{\text{Total body burden of } ^{137}\text{Cs} (\text{pCi})}{\text{Body weight (kg)} \times ^{137}\text{Cs in blood (pCi/kg)}} \]

Conclusively, the assessment of total body burden of \(^{137}\text{Cs}\) in people can be made basing upon the analysis of blood by the use of the factor \(f\) as being 6, provided the daily intake varies with rates not exceeding those described in this report. Parallel determinations of the body burden and blood level on control subjects on the basis of which the relation factor at that time is determined as was the case in previous studies\(^1,2,13\)) can be omitted. In such an assessment, possible errors would amount up to 30% in individual determination but the use of a pooled blood sample representing a large number of individual can afford a means of assessing the population level with a satisfactory precision.

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