INTERNAL DISTRIBUTION OF URANIUM COMPOUNDS IN THE BODY AND ITS ACUTE POISONING

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For the purpose of obtaining some basic data on the radiobiological effect of uranium, experimental studies on acute poisoning by uranium compounds and internal distribution of soluble uranium in the body of animals were undertaken.

METHODS AND RESULTS

A) Distribution of Soluble Uranium in the Body.

According to our preliminary study[16], the lower measurable limit of radioactivity of uranium was found to be about 5 mg in the form of uranyl nitrate mounted on a measuring slide, when a scintillation counter was used. Nevertheless that measurable limit by a GM-counter is about of 0.5 mg of uranium nitrate. Because of difficulty in counting alpha-rays by the scintillation counter, dosimetry of uranium was thus performed usually with a GM-counter.

In this study measurement of radioactivity was carried out when the background gave values of within 20 ± 0.5 cpm.

As a first step a suitable quantity of precipitator was searched. Into each of eight test-tubes containing 5 mg of uranyl nitrate solution, 0 ccm, 1 ccm, 2 ccm, 3 ccm, 4 ccm, 5 ccm, 6 ccm and 7 ccm of aluminum nitrate solution were added respectively as precipitator for the uranium solution. Ammonium hydroxide was next added to each of the test-tubes until the reaction became neutral or weak alkaline. Each material, then, was transfused into the filtrator attached with a filter paper at the bottom. After precipitation and drying, the materials were counted. Thus, 3.5 mg of aluminum nitrate was considered to be an adequate amount of precipitator for uranium measurement (Fig. 1).

Secondly, the relationship between quantity of uranium in the material and counting values was studied. Various amounts of soluble uranium in the test-tube were treated by the same procedure as above. Results thus obtained were plotted on the curve shown in Fig. 2. From 0.5 mg up to 20 mg the curve is linear, but when the material contained over 20 mg of soluble uranium there was not seen the linear relationship between the quantity and count value, because of self-absorption.

Next, 20 mg of uranium nitrate in an aqueous solution of 1 ccm were injected into the peritoneal cavity of adult male rats, and the animals were

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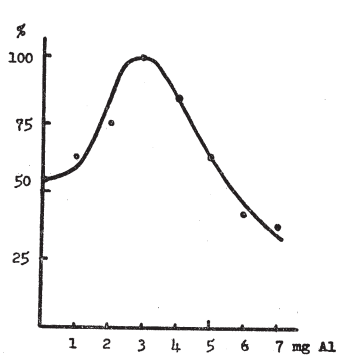

FIG. 1

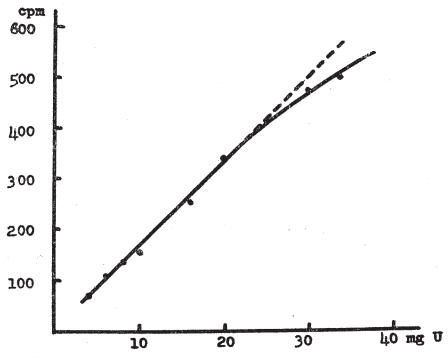

FIG. 2

FIG. 1. The relationship between the quantity of precipitator for uranium analysis and counting values.

FIG. 2. The relationship between the dose of uranium in the material and counting values.

sacrified 6, 24 and 48 hours after the injection. Though the experiment was planned with 72 animals, all died approximately within 50 hours after injection. In each group, the liver, spleen, testes, muscles, bones, adrenal glands, and blood were treated and counted. Each of these organs was made into moist ashes in a crucible by dropping concentrated nitric acid, followed by the same chemical procedure as described above.

The results are shown in Fig. 3. It is noteworthy that the concentration of uranium in the bones and kidneys gradually increased with lapse of time, while the uranium concentration in the blood decreased rapidly approximately proportionally with that in the liver, spleen and muscles.

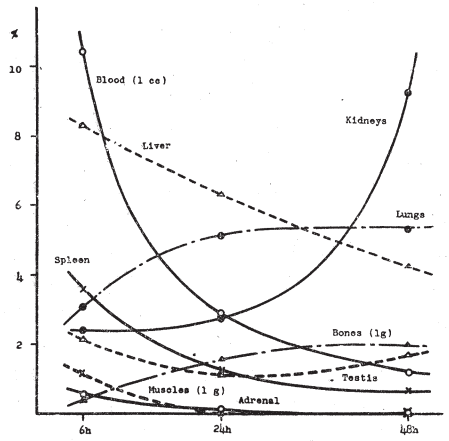

FIG. 3. The distribution of uranyl nitrate in the animals when 20 mg of uranyl nitrate were injected into the peritoneal cavity of rat. The figure shows that the relationship between the percentages of uranium fragmentation in each organ and the elapsed time after the treatment.

B) Histological Study of Acute Soluble Uranium Poisoning.

Five mg, 3 mg, 1 mg, 0.5 mg and 0.1 mg of soluble uranium were injected into the peritoneal cavity of adult male rats. The animals were sacrified 2 hours, 6 hours, 24 hours, 48 hours, 3 days, 1 week, and 3 weeks after injection. The various organs of the body were examined microscopically.

In the 5 mg injected group, there were some bleeding and lymphocytic infiltration in the glomeruli of the kidney 6 hours after injection. Bowman's capsule, however, remained normal. Some hyperemia and bleeding were seen in the renal stroma resembling hemorrhagic nephritis without cell atrophy. The epithelial cells were turbid and some appeared to have been shed into the lumen mainly in the straight portion of the renal tubule. Neither nuclear pyknosis nor vacuole formation of cytoplasma was seen.

In the lungs, some lymphocytic infiltration was recognized in the stroma. Other organs such as the liver, spleen, heart muscle, and testes appeared approximately normal except for some hyperemia. All animal in this group died nearly 30 hours after injection, when renal bleeding somewhat increased than that seen at the sixth hour and the epithelial cells appeared swollen. These changes resembled regressive degeneration. In the liver and spleen no parenchymal change was observed. In the small intestine slight bleeding in the submucous tissue and some destruction of the epithelial cells of the intestinal villi were seen, though the goblet cells remained normal.

In the 3 mg injected group, the histological findings at the end of 24 hours showed almost the same appearance as those of the 5 mg injected group at the 6th hour. Animals died with in 50 hours after the injection.

In the 1 mg injected group hyperemia in the tissue was observed in the kidneys since the 2nd hour of injection, though degeneration of the epithelial cells of the renel tubuli started at the 24th hour, and gradually increased up to about 1 week after injection. No glomerular change was observed in this group.

In the 0.5 mg injected group degeneration of the epithelial cells was first seen 1 week after injection, which, however, was not exaggerated with time.

In the 0.1 mg injected group no degenerative change was observed in the kidneys, with the exception of some hyperemia 72 hours after injection. However, at the end of the 3rd week abnormalities were seen neither in the kidneys nor in other organs.

C) Acute Poisoning due to Insoluble Uranium.

For this study uranium bioxide was used. As shown in Fig. 4, the average particle size of this powder was almost 0.1 micron. Adult male rabbits were made to inhale uranium particles with a special syringe through the operatively exposed trachea.

The rabbit which inhaled 1000 mg of this agent died 4 days after the operation. Microscopically examined the uranium particles were distributed relatively evenly up to the peripheral part of the lung. There were found massive infiltration of leukocytes, proliferation of the septal cells and moderate hyperemia, associated with some exudation in the alveoli. The particles were

not phagocytised. No fibrous change was present. Other organs such as the stomach and liver appeared normal. Radioautographically, however, some alpha-tracks were imaged on the slide of the heart muscle as shown in Fig. 5. It was believed that some particles entered the blood stream.

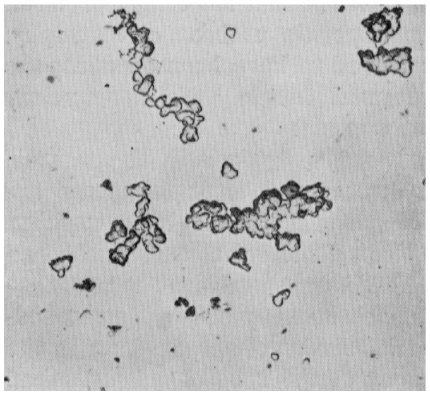

FIG. 4

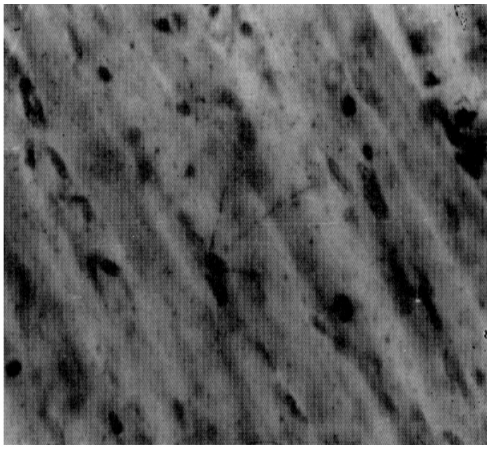

FIG. 5

FIG. 4. The replica photograph of uranium bioxide particles used in this study. 7 000 times magnification.

FIG. 5. Radioautogram of the heart muscle of the rat inhaled 1 000 mg of insoluble uranium. Several dotted lines show the alpha-tracks from uranium.

The rabbits which inhaled 300 mg of uranium bioxide died 1 week later. The histological findings of this group were approximately the same as those of the 1 000 mg inhaled animals, except for less hyperemia in the lungs.

On the other hand rabbits which inhaled 100 mg of insoluble uranium were apparently healthy and survived till the end of the fourth month, with normal hematological data and usual growth rate. One rabbit of this group was sacrified for histological observation. In the lungs there were seen some foreign bodies resembling uranium particles, slight proliferation of the septal cells, and slight infiltration of lymphocytes and granulocytes. Also some exudation and phagocytes were present. On the slide treated with Van Gieson's stain a very slight fibrous proliferation was seen adjacent to the area of leukocytic infiltration. The other organs appeared normal.

DISCUSSION

Donney[5] observed that intraperitoneal administration of soluble uranium induced acute nephritis and glucosuria within a short time. Dinse[4] stated that uranium of more than 0.08 mg/kg caused various degrees of renal disease. Neuman[15] studied in detail the distribution and excretion of hexavalent uranium compounds in animals. Our experimental results coincided closely with these reports.

According to our data, the amount of uranium fragmentation taken in the liver, spleen, testes, adrenal glands, etc., ran approximately parallel with that in the blood. This indicates that uranium was contained in the blood stream rather than in parenchymal cells.

Barnett[1] stated that renal injuries due to soluble uranium consist mainly of epithelial degeneration and necrotic change of the renal tubuli. In our results renal bleeding was also recognized in a relatively early stage, possibly due to uranium dose in excess. According to Stockinger, deposition of insoluble uranium in the lungs of rats increased with the decrease in average size of particles[21]. La Belle described that a moderate kidney injury was found in animals which were made to inspire uranium particles of 0.5 microns in average diameter[11]. Wilson also obtained similar results, using dusts of Carnostone containing 20 per cent uranium[27]. In our experiment particles under 0.5 microns in size were used, but no definite renal disease was detected. However, this does not entirely deny the possibility of renal disorder, because we did not carry out urinalysis before the death of animals. In Blair's opinion, UO_2 itself is not toxic for the living body, but secondarily produced uranyl ions are harmful[2]. Therefore the α-ray of uranium detected by us in the heart muscle radioautographically possibly changed its original insoluble agents into such a chemical form.

The blood picture was not abnormal during the four months. This is probably because the too low radiation dose failed to injure the blood forming organs.

CONCLUSIONS

1) The present paper deals with an experimental study on the fate of uranyl nitrate introduced into the peritoneal cavity of rats, and acute poisoning of animals with this agent.

2) Quantity of uranium in the body of animals was measured by counting the beta-ray emitted from uranium.

3) Uranium concentration in the blood was maximum at six hours after injection, and then gradually decreased. Uranium deposition in the liver, spleen, adrenal glands, and muscles changed its value in parallel with that in blood. In the kidneys, however, uranium fragmentation gradually increased with time till up to 9 per cent of the injected dose at the end of 48 hours. The same tendency was seen also in the bone.

4) Rats injected 0.05 mg/g of soluble uranium intraperitoneally all died within about 30 hours after injection. Microscopically, moderate hyperemia and bleeding in the stroma and hyaline degeneration of the epithelial cells in the renal tubuli were seen in the kidneys.

5) In the group of 0.001 mg/g injection, renal changes were very slight, and complete recovery was seen after about three weeks.

6) Rabbits made to inspire 1 000 mg and 300 mg of insoluble uranium died about 4 to 7 days after the inhalation. However rabbits which inhaled 100 mg of insoluble uranium survived for more than 4 months. In this group growth

rate and hematological findings were normal. Four months after the treatment one of these rabbits was sacrified and examined microscopically, but no definite changes were found in the lungs and kidneys.

7) In the heart muscles of rabbits which inhaled 1 000 mg of insoluble uranium some alpha-tracks were detected radioautographically, which indicates that some uranium dusts might have been taken up into the blood stream.

REFERENCES

1. BARNETT, T. B.: cit. 24.
2. BLAIR, H. A.: *Uranium, Quarterly Technical Report*, Jan-Mar. 1953.
3. CHIKUSAN-SHIKENJO: *Chikusan-Shikenjo Shuho* **37**: 27, 1940 (Japanese).
4. DINSE, A. G.: AECD-2770, Dec. 22, 1949.
5. DONNEY, G. L. *ET AL.*: *Proc. Soc. Exper. Biol. Med.* **57**: 75, 1944.
6. DOWN, W. L. *ET AL.*: AECD-2272, Dec. 22, 1949.
7. EVERSOLE, W. J.: LA-1333, 1953.
8. HODGE, H. C. *ET AL.*: AECD-2784, Dec. 22, 1949.
9. KAGAKU-GIJUTSUCHO: *Hoshasen-Sokuteiho*, Tokyo: 1957 (Japanese).
10. KITABATAKE, T.: *Nagoya J. med. Sci.* in press.
11. LA BELLE, C. W. *ET AL.*: UR-197, June 6, 1952.
12. MASTURZO, A.: *Folia Med.* **33**: 643, 1950.
13. MASTURZO, A.: *Folia Med.* **33**: 748, 1950.
14. NEUMAN, W. F.: cit. 24.
15. *National Beaureau of Standard, Handbook*, **52**: 1954.
16. OKAJIMA, S., T. KITABATAKE AND T. KATAYORI: Read at the 6th Meeting of Tokai-Hokuriku Radiology Society, 1958.
17. PASSALACQUA, F. *ET AL.*: *Fortschr. Röntgenstr.* **84**: 609, 1956.
18. *Report of Japan Atomic Energy Institute* 1, 1957 (Japanese).
19. SHIBATA, Y.: *Uran*, Tokyo: Maruzen, 1956 (Japanese).
20. SPECTOR, W. S.: *Handbook of Toxicology* Vol. 1, Philadelphia: W. B. Saunders Co., 1956.
21. STOCKINGER, H. E. *ET AL.*: *Arch. Ind. Hyg. Occupational Med.* **4**: 346, 1951.
22. STOCKINGER, H. E.: AECU-669, Dec. 22, 1949.
23. TAKAHASHI, S., T. KITABATAKE AND T. YAMAGUCHI: Report to Committee on Maximum Permissible Dose in Japan, 1958 (Japanese).
24. VOEGTLIN, C. AND H. C. HODGE: *Pharmacology and Toxicology of Uranium Compounds.* New York: McGraw-Hill Co., 1949.
25. WATANABE, K.: *Tohoku J. Exper. Med.* **63**: 251, 1956.
26. WATANABE, K.: *Tohoku J. Exper. Med.* **66**: 131, 1956.
27. WILSON, H. B.: *Arch. Ind. Hyg. Occupational Med.* **7**: 301, 1953.
28. WINTOROBE, M. M.: *Am. J. Phys.* **114**: 502, 1935.