RESPONSE OF HUMAN BEINGS ACCIDENTALLY EXPOSED TO SIGNIFICANT FALL-OUT RADIATION (SUMMARY)

Naval Medical Research Institute, Bethesda, Maryland, U.S.A.
and U.S. Naval Radiological Defense Laboratory
San Francisco, California, U.S.A.

Dr. R. A. Conard reported observations made by himself in collaboration with Dr. E. P. Cronkite, Dr. V. P. Bond, Lieut. N. R. Shulman, Dr. R. S. Farr, Dr. C. L. Dunham, Dr. S. H. Cohn and Lt. Col. L. E. Browning.

Marshallese islanders and some American servicemen were exposed to fall-out radiation which followed the detonation of a thermonuclear device. Sixty-four persons on the island which received the heaviest fall-out were exposed to about 175r units of penetrating γ-radiation and a large dose of β-radiation on parts of the body not covered by clothing.

The group were first examined a few days after exposure, and observations were made during the course of the next year.

The blood changes were as follows:

Absolute neutrophils. Count fell to 50% of normal in the sixth week. Recovered slowly, but was normal after one year.

Absolute lymphocytes. Count fell to 55% (25% in children) of normal value, was still low at six months and somewhat below normal at one year.

Platelets. Count fell to 30% of normal value at fourth week. By six months it was 70% of normal and by one year still slightly below normal.

Comparison of the haematological data with data from cases in Hiroshima and Nagasaki made it seem likely that if this group had received an addition of 50–100r some fatalities might have occurred.

Skin lesions. The great majority of the group of 64 people showed skin lesions, but only 20% of these were severe. Among the severe cases wet desquamation was seen which resulted in weeping ulcers; most of them healed in about ten days. Foot lesions were among the worst and were quite painful. Vesiculation was seen here, and ulcers remained after the blisters ruptured. At six months these were completely healed, but showed some lack of pigmentation.

Internal hazard. Internal absorption of radioactive material (measured by analysis of urine) was too low to have contributed significantly to the acute radiation syndrome. The amount and type of the radioactive materials absorbed make significant long-term effects unlikely.

The general health of the group after one year was good; four pregnancies had terminated in normal births of apparently normal babies and new pregnancies were in evidence.

Discussion

Mitchell. Can you estimate approximately the β-ray doses for dry and moist desquamation under these conditions?

Conard. Unfortunately there is such a wide spectrum of β-ray energies involved in this fall-out material that an accurate estimate of the skin doses is impossible.

Mitchell. Could I ask what is your guess?

Conard. I would guess 5,000 rep or more.

Ellis. Was there any evidence of assimilation of any radioactive material by inhalation or ingestion?

Conard. Most of the internal absorption was through ingestion. The people lived in open-type houses, and the food and their drinking water were highly contaminated. There was probably less hazard from inhalation than there was from ingestion. This was also shown by the fact that the faeces contained a considerable amount of activity.

Ellis. Was there any ingestion of long-lived isotopes?

Conard. There must have been some long-lived material, but I think this was minimal. Any long-lived activity which they have ingested is certainly below tolerance levels. Numerous urine samples were examined at frequent intervals, and there was activity present. Careful analysis revealed that the limits of exposure were below the maximum permissible dose.

Phillips. Can you say if there were any significant amounts of iodine in any form?

Conard. There was, no doubt, a considerable amount of iodine in the early stages, and it is estimated that the thyroid glands received at least 100 rep from the iodine.

Question. This is not a radiobiological question, but can you say how far from the centre of the explosion these cases occurred?

Conard. The closest people were a little over 100 miles from the explosion I believe.

FIG. 1. Neck lesions at 28 days. Wet desquamation. White colour is calamine lotion. Case 78, age 37, F.

FIG. 2. Hyperpigmented raised plaques and bullae on dorsum of feet and toes at 28 days. One lesion on left foot shows deeper involvement. Feet were painful at this time. Case 67, age 14, F.

FIG. 3. Epilation in 7-year-old girl at 45 days. Case 72.

FIG. 4. Extensive lesions in 13-year-old boy at 45 days post-exposure.

Mole. Can I ask Dr. Conard if the secondary fall in platelets, shown in his diagram to occur between the 50th and 60th day, was a real fall, and if so if he has any explanation for it?

Conard. Yes, I think this is a real fall. The platelet counts were very consistent on an individual basis, and on an individual basis they all showed a primary dip followed by the secondary dip. I do not know what the explanation is. But we felt that the platelet counts were the best index of the degree of radiation damage because of their consistency, whereas the white counts showed considerable fluctuation from day to day. The platelet counts were very consistent.

Thea Houtermans. How many days after the accident was the first analysis of urine made?

Conard. I do not know whether I can recall this accurately, but I think it was about two weeks after the accident. It may have been 11 days. I am not positive on that point.

Rothblat. I believe you said, Dr. Conard, that if these people received a dose of about 50r or 100r more there would have been fatalities. I wonder on what basis you state this. We happen to know from a few accidents which occurred in other places that people can receive up to 450r and they still have recovered from the irradiation.

Conard. I meant the minimal lethal dose. The calculation was based on the comparison of Japanese groups who sustained some fatalities. This was the group receiving the lowest dose which sustained mortalities and showed definite evidence of radiation effects among the Japanese.

Rothblat. Would you say that in the case of reactor accidents the difference is as between external radiation there and ingestion and inhalation here?

Conard. We thought that the internal dose did not add significantly at all to the total body radiation picture—it was too small.

ACUTE LEUKAEMIA AND OCCUPATIONAL RADIUM AND RADON EXPOSURE

JOHN D. ABBATT
Hammersmith Hospital, London, England

Introduction and occupational history

It has recently been possible to observe during his terminal illness a male patient who had been occupationally exposed to radium for at least 35 years.

TABLE I

Representative Record of Routine Serial Blood Counts

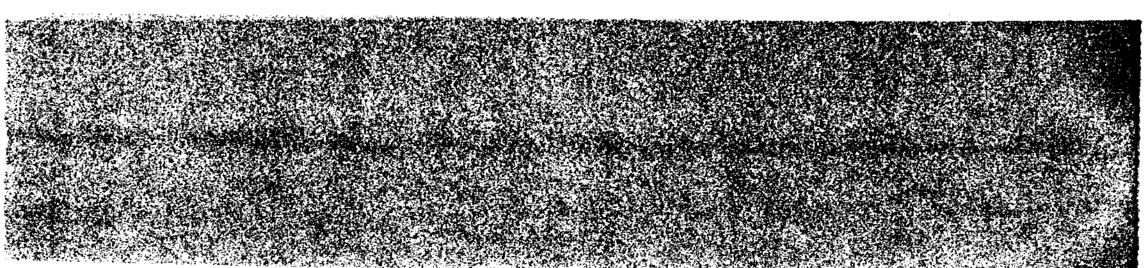
Date	Hb (%)	R.B.C.	W.B.C.	Neutro-phils	Lympho-cytes
30.6.19	—	—	2,550	1,785	714
24.7.19	—	—	3,200	2,048	1,024
4.9.19	—	—	4,300	2,343	1,613
28.11.19	105	5,272,000	—	—	—
8.9.21	103	4,912,000	5,010	3,225	1,685
29.1.24	99	4,772,000	5,860	3,320	2,220
14.3.27	—	—	5,560	3,560	1,920
3.1.30	—	—	6,840	5,040	1,720
15.3.33	—	—	8,000	6,000	1,760
13.2.36	—	—	4,760	3,600	1,080
25.2.36	85	4,300,000	6,320	3,840	2,080
10.6.36	—	—	4,640	2,880	1,680
4.8.36	95	4,000,000	5,120	3,680	1,200
16.12.36	97	3,700,000	7,200	4,560	2,480
14.6.39	—	—	5,760	3,040	2,640
26.7.39	—	—	6,240	3,200	2,800
9.12.49*	100	—	3,300	2,700	430
30.4.54	45	—	—	—	—
18.5.54†	34	1,900,000	10,800	5,200	4,300
		(also 3% blasts and 5% metamyelocytes)			

* Blood count performed while in hospital for surgical relief of benign intestinal obstruction.

† Blood counts performed by patient's private doctor.

FIG. 1. The patient's right and (Fig. 2) left hands, showing digital amputations, radiation hyperkeratoses and other skin changes.

Fig. 2



The patient was first associated with ionising radiations about 1904, when he was examining the feasibility of extracting radium from Cornish uranium deposits. He later became concerned with the preparation of radon and radon solutions from a source of radium salt in solution which varied from 1·0 to 1·5 gm. This latter occupation covered the period from 1911 to 1939, when the patient retired. From the information available to us about conditions in his laboratory and the date of much of his work, it is probable that such radiation protection as was adopted would now be considered very inadequate.

Summary of medical history

In general, this patient's health throughout his life was good and his death from acute leukaemia at the age of 74 after a relatively short illness indicates that his life span was not unduly, if at all, shortened by his occupation. It should, however, be noted that the patient quite frequently took long vacations when his blood count was considered to be abnormal. In 1936 a marked but transient anaemia was first manifest (Table I), and the patient nominally ceased his active radon work.

Areas of hyperkeratosis were first noted by the patient on his fingers in 1914. On unknown dates, but between 1920 and 1939, amputations of the left index finger, right thumb and part of the right index finger were performed.

The patient's terminal illness was first clinically obvious in April 1954, and his general condition deteriorated fairly rapidly and he died in mid-June 1954 of acute leukaemia after a clinical illness of only a little over two months.

Clinical and Pathological Investigations performed during the Patient's Terminal Illness in Hospital

On clinical examination the patient was frail and anaemic, with a retinal haemorrhage in one eye and numerous petechiae. The liver, spleen and lymph glands were never clinically enlarged. The hands showed evidence of gross radiation damage (Plates I and II). X-ray examination of the skeleton showed a generalised decalcification with localised areas of osteolysis.

A number of blood counts were performed while the patient was in hospital (Table II).

The sternal marrow was biopsied and yielded visible fragments of cellular marrow which showed marked hyperplasia with erythropiesis predominating, and many abnormal megaloid erythroblasts. Leucopoiesis was defective with an excess of myeloblasts. A differential count gave the following figures:

Erythroblasts 64% Myeloblasts 13% Other leucocytes 23%

These findings indicate a leukaemia of the erythromyelosis type.

TABLE II

Peripheral Blood Counts, 25.5.54 to 11.6.54

Haemoglobin and red cell series							
Date	Hb (%)	R.B.C.	P.C.V.	M.C.H.	M.C.H. Co.	M.C.V.	Retics
25.5.54*	33	1,500,000	16	32	30	107	2·5
31.5.54†	43	2,300,000	22	28	29	96	1·6
3.6.54	68	—	—	—	—	—	—
7.6.54	72	—	—	—	—	—	—
8.6.54	55	3,000,000	27	27	30	90	0·8
11.6.54	39	2,000,000	19	29	31	95	0·4

White cell series and platelets											
Date	W.B.C.	Blasts	Promyelocytes	Myelocytes	Metamyelocytes	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	Platelets
25.5.54	3,700	518	—	74	962	666	111	—	1,258	111	—
31.5.54	5,000	850	50	200	250	2,000	250	100	1,200	100	20,000
7.6.54	3,500	—	—	—	—	—	—	—	—	—	—
8.6.54	3,400	136	34	68	136	2,652	—	34	238	68	40,000
11.6.54	2,800	—	—	—	—	—	—	—	—	—	40,000

* Nucleated red cells 12/100 white cells. Examination of the blood film showed the presence in the red cells of macrocytosis, hypochromasia, polychromasia, marked anisochromasia and frequent poikilocytosis.

† Nucleated red cells 11/100 white cells.

At post-mortem Professor Harrison's comment was "The findings in the bone marrow and spleen together with the blood findings during life indicate that death was due to acute myeloid leukaemia."

Physical measurements relating to body radioactivity

Physical measurements were made of the radon content of the expired breath during the month before death and of the whole body radioactivity.

On three days while the patient was in hospital samples of expired breath were collected and measured in a high-pressure ionisation chamber. The

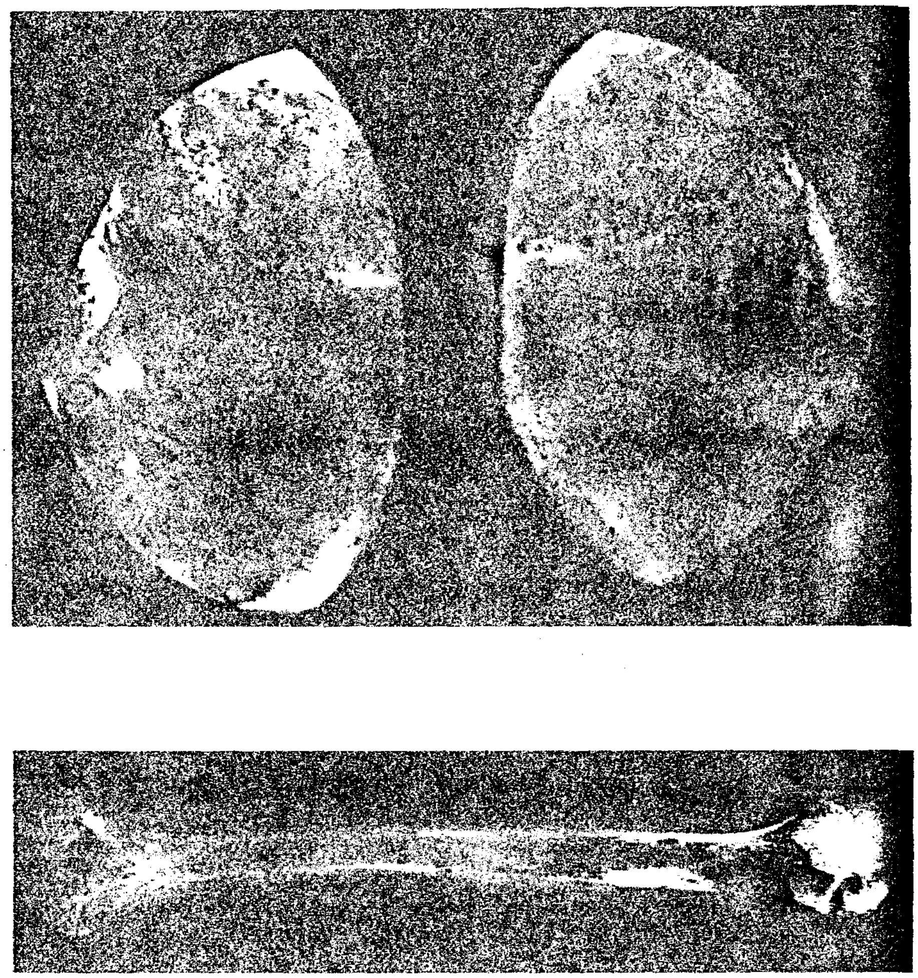
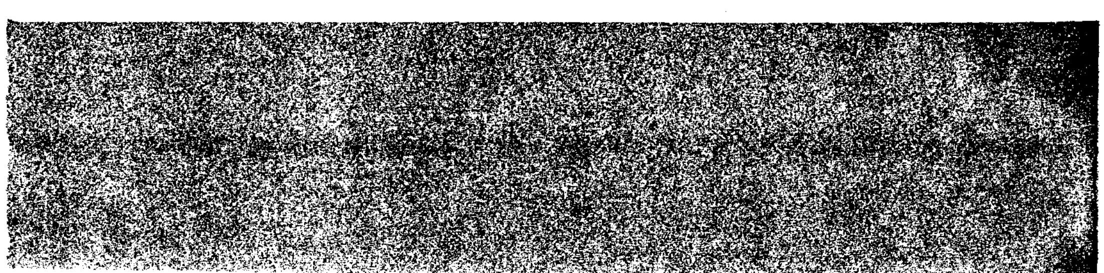


FIG. 3. Above: Post-mortem radiographs of two portions of the patient's calvarium, showing radiographic changes. Below: Post-mortem radiographs of the patient's humerus, showing similar radiographic changes, i.e. osteolysis, etc., to those seen in the calvarium.



values obtained were in good agreement with one another and showed a mean radon concentration of $4 \cdot 4 \times 10^{-12}$ C./litre, compared with a control sample obtained from a member of the hospital staff of $2 \cdot 3 \times 10^{-13}$ C./litre.

Measurement of the γ-ray emission from the whole body was made, and after correction for the body potassium content, if the excess activity was due to radium then 0·166 μgm. was the mass of radium which was in equilibrium with the retained radon fraction in the body.

The magnitude of the excreted radon fraction was estimated by measuring the total activity at radioactive equilibrium of a representative selection of bones obtained at autopsy. In the course of these measurements it was observed that the increase in γ-ray emission for the bones as radioactive equilibrium was reached was due to radon, and it was considered probable that the whole excess γ-ray activity was due to radium. Absolute activities were obtained by calibration. The total skeletal radium content at equilibrium was estimated to be 0·478 μgm., and since the measurement of the radium in the whole body was 0·166 μgm. and corresponded to the retained radon fraction the excreted radon fraction = 0·478 − 0·166 μgm. i.e. 65%. This is a figure considerably higher than that usually quoted, but may be accounted for by the nature of the terminal illness and the state of the bones at the time of measurement, i.e. one of marked decalcification, with marked marrow hyperplasia. Moreover, a figure of 65% for the radon excretion fraction agrees well with the radon in breath measurements made shortly before the whole body activity measurements if a normal air exchange is assumed.

Discussion

The aetiology of leukaemia is still unknown, though certain agents are known to be leukaemogenic. In particular, ionising radiations have been shown in both man and animals to produce increases, sometimes marked, in the incidence of leukaemia in irradiated populations. However, in any individual case which develops leukaemia it is not yet possible to do more than regard any irradiation received prior to the development of the disease as being a possible factor in the development of that disease. In the patient whose case has been presented it is precisely because we are unable to determine the part played by irradiation in his story that it is considered to be of value. It is clear that despite a reasonably detailed study there remain many unanswered and probably now unanswerable questions about this patient's radiation dosage. But even if an accurate statement of radiation dose were available, we are not yet in a position to decide its significance, since the human (and animal) dose-response relationship for leukaemia induction is not yet accurately known. In particular, the effects of a combination of partial body external irradiation and chronic internal irradiation are quite unknown.

The patient undoubtedly had received a very considerable dose of external irradiation from radium during his working lifetime of 35 years, and his hands bear eloquent testimony to this exposure. Since his work was concerned with radium and the preparation of its daughter products, there is little doubt that much of the hand damage resulted from β-irradiation. However, it is probable that he received a considerable whole body dose spread over a long period of time—exactly how large this dose was will never be known. But by 1919 it is probable that appreciable irradiation had occurred, since hand damage was first visible in 1914 and leucopenia was first recorded in 1919 and may have been present in 1914.

At the time of death from acute myeloid leukaemia in 1954, i.e. 15 years after retirement, there was a skeletal radium content of 0·5 μC. radium. The breath radon measurements made during the month prior to death indicated that a breath radon excretion of approximately 60% was occurring at least during this period.

All biological organisms in health are in a state of dynamic equilibrium, so that when unstable bone-seeking elements such as radium are considered, a single measurement of the "fixed skeletal burden" gives only a very limited amount of information. In particular, no indication is given, or can be obtained, of the total ingested, inhaled or injected activity, nor of excretion.

The concept of a maximum permissible tolerance dose or burden of radiation or radioactivity involves a risk which in the words of the I.C.R.P. "is small compared to the other hazards of life" (Int. Comm. on Protn., 1954). In view of the increasingly widespread use of radiation and radioactive materials it is important that this risk should be evaluated in both a qualitative and quantitive manner. This can never be achieved by the study of single individuals or groups, whether they be cells or men, and the patient whose story has been described illustrates some of the limitations of the study of individuals, since the only change present which can definitely be ascribed to irradiation is the hand damage, and that only on a qualitative basis.

Before such conditions as leukaemia, tumours, a shortened life span or genetic changes can be ascribed to irradiation in particular groups, large-scale studies of irradiated populations under known conditions must be undertaken. Some of the techniques and difficulties involved in such studies are discussed in another paper which is being presented at this meeting (Court Brown). The value of such studies is greatest in precisely those groups involving irradiation at or near the present maximum permissible tolerance level, as in the patient described. Not only is it necessary to confirm the validity of the present maximum permissible tolerance levels, but the changes which may be expected to occur near the "tolerance" levels are likely to be particularly fine and subtle in character.

Acknowledgments

I would like to express my sincere thanks to a number of colleagues for their help in the investigation of this patient and for permission to quote some of their findings. In particular I would like to thank Dr C. Cope, Dr. W. M. Court Brown, Dr. P. R. J. Burch, Dr. J. V. Dacie, Professor C. V. Harrison, Professor F. W. Spiers and Dr. R. C. Turner.

REFERENCES

COURT BROWN, W. M., 1955. "Some Observations on the Occurrence of Leukaemia in an Irradiated Human Population." Paper given at the International Conference on Radiobiology, Cambridge.

International Commission on Radiological Protection, 1954. *Brit. J. Radiol. Supplement*, 1955, p.10.

DISCUSSION

Muth. These results recorded by Dr. Abbatt are very important because any results found for man are of much more value than results of the most careful experiments made on animals. We have had the opportunity of making measurements on radium-poisoned persons too during recent years. There were three cases of radium poisoning which ended fatally. There were two chemists in the Frankfurt region of Germany. In one of these cases we found a radium deposit of $3\text{–}4 \times 10^{-6}$ gm. of radium; he died from aplastic anaemia ten years after having ingested the radium. He had not been very cautious when he first commenced his work in an industrial firm, and during the first few weeks he ingested an amount of radium leading to this burden, $3\text{–}4 \times 10^{-6}$ gm. of radium. We could not find very much radon in the expired air, and I think that the value given by Dr. Abbatt is a very high value. It seems that these values are very different from person to person. Another case, also a chemist, died from radium poisoning. The measurements on this case are in progress. We found that, according to preliminary results, he had $1\text{–}2 \times 10^{-6}$ gm. of radium deposited in the body. All these cases had fibrosis of the lungs too, and I would ask Dr. Abbatt if he found such fibrosis in his cases. Another case which we are measuring was a radium poisoning case in Berlin. He had lung carcinoma following inhalation of radium dust in his laboratory over a long period. We have made some autoradiographical measurements and we find that he had a very high deposit in the lungs. These deposits and concentration of radium particles in the lungs are the cause of lung cancer.

Abbatt. The question about fibrosis of the lung in association with the radium poisoning may well be true of atmospheres where there is a high dust content, as in the Joachimstal cases; but in our patients, where the path of entry has been ingestion rather than inhalation and has not been associated with a high dust content, we have not found gross fibrosis. The other slightly different problem, of the aetiology of lung cancer and high dust contents with radon and daughter products associated with the dust, is, I think, a most important suggestion, but I think that it is again one which we should not conclude is true from single cases. I think we should treat it in exactly the same way and analyse it on a statistical basis from population surveys with detailed analyses of statistically selected samples from that population.

Rajewsky. I have investigated very many of several hundred cases in Schneeberg and St. Joachimstal. They all died of carcinoma of the lung, and it is interesting that leukaemia occurs relatively seldom in these cases.

Abbatt. Is it possible that these patients did not survive long enough to develop leukaemia?

Rajewsky. The mean working life time of these miners is 10 to 15 years. After this time they develop carcinomata. It should be long enough for leukaemia to develop.

Abbatt. I still feel we do not know. We do not know how long it takes, with these low dose chronic burdens, for the development of leukaemia if, in fact, the disease described is irradiation leukaemia. I still feel that the population surveys are necessary.

Popjak. You showed on one of your lantern slides a picture of the bones, and I particularly remember the skull. Were those deficiencies in the skull due to leukaemic deposits, or were they caused by radium damage? Secondly, have you any further autoradiographic examinations of the bones to see in what particular part of the bones the radium was deposited?

Abbatt. The question of the holes in the bones is extremely difficult when associated with leukaemia. That type of change has been noted in other radium poisoning, not necessarily associated with leukaemia but usually associated with some type of bone marrow damage. I think the answer is that whether the osteolytic areas are primarily due to radium or due to secondarily diseased process produced by radium, cannot be actually decided in detail or with any degree of accuracy. The second part of your question on autoradiographic studies: they are under way. Dr. Vaughan is doing some in considerable detail, and we already have a number of pictures and autoradiographs made at the Royal Marsden Hospital, but I do not feel that I am willing yet to comment on them because I am not in possession of all the data. It might be misleading to comment at this stage.