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COMPARISON OF ACUTE AND CHRONIC CHANGES PRODUCED IN RATS BY IODINE-131 AND ASTATINE-211 AT LETHAL LEVELS. PRELIMINARY CLINICAL DATA ON THE UPTAKE OF ASTATINE-211 IN PATIENTS WITH THYROID DISEASE

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THE first studies with radioactive iodine demonstrated the selective accumulation of ^{128}I in the thyroid gland of rabbits[1]. (See Appendix I.) Subsequently the excretion and uptake of ^{131}I by the thyroid gland were studied on patients having different types of disorders of that organ including thyroid carcinoma. The excretion studies were performed on normal subjects and showed the fraction eliminated to be in the range of 81 per cent to 53 per cent in the first 24 hours following oral administration. These experiments included not only a quantitative determination of the accumulation of ^{131}I but also the stable iodine content of the thyroid gland in various types of goitre. The thyroid tissue was obtained[3] by surgical removal of that organ 24 to 48 hours after administration of ^{131}I. Detailed ^{131}I tracer studies in the rat have been made by several investigators including H. W. JOHNSON and A. J. ALBERT[4] and J. G. HAMILTON *et al.*[5].

Apart from the thyroid gland, relatively limited effort has been directed towards a study of acute and chronic effects induced by massive doses of carrier-free ^{131}I in experimental animals. A study has been made of the destructive action of ^{131}I in the mouse. When the amount administered subcutaneously reached a level of 20 μc/g or greater, the animals usually did not survive for more than one month. This particular experiment was primarily concerned with injury to the thyroid gland and was not devoted to any gross or microscopic pathological changes in other tissues and organs[6].

Extensive studies have been done by R. C. GOLDBERG *et al.* in the rat which were directed towards observation of the acute and chronic effects upon the thyroid gland following large amounts of ^{131}I. These investigators employed dose levels up to approximately 5 μc/g using Long–Evans rats and their period of investigation extended from three days to eight months. They noted that high dose levels produced complete obliteration of the thyroid gland with some injury to the parathyroid gland. They also observed changes in the pituitary gland which may be presumed to be the effect of prolonged

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ablation of functional thyroid tissue[7]. Myxoedema has also been demonstrated in ^{131}I thyroidectomized dogs[8].

Element 85, which is a radioactive halogen, was discovered in 1940 and was named astatine by D. R. Corson, K. R. Mackenzie and E. Segré[9]. Twenty radioisotopes of astatine have now been identified. There are no known stable isotopes of this element. The radioisotope of astatine employed in these experiments is ^{211}At which has a half-life of 7·3 hours. (See Appendix II.)

The chemical preparation and properties of astatine are very complex. Astatine under certain conditions behaves like a heavy metal such as bismuth, mercury, silver, antimony[10]. When the first attempts were made to isolate and identify astatine, tracer studies were initiated employing guinea-pigs as the experimental animals. In view of the position of astatine in the Periodic Table, special attention was directed towards the possible selective accumulation of this radiohalogen by the thyroid gland. Control animals and those in which thyrotoxicosis had been induced by the administration of the thyrotropic hormone were used. These animals received both ^{131}I and ^{211}At at the same time so that a direct comparison could be made between these two radiohalogens in the same tissues and organs. While the accumulation of ^{211}At by the thyroid gland in both groups of guinea-pigs was roughly a quarter of that of ^{131}I, this experiment demonstrated[11] a high degree of selective localization and retention of ^{211}At. Later more detailed tracer studies with carrier-free ^{131}I and ^{211}At were performed on rats. In these experiments ^{131}I and ^{211}At were administered intravenously and the accumulation of ^{211}At by the thyroid gland was observed to be one tenth of that of ^{131}I at time intervals ranging from one to 72 hours. This type of dual tracer experiment was possible because of the fact that the α-particles of ^{211}At could be counted in an ionization chamber insensitive to the ^{131}I β-particles which later were measured with a Geiger–Müller counter. In this series of experiments the metabolism of astatine in tissues, other than the thyroid gland, was found to be very similar to that of ^{131}I at five time intervals ranging from one to 24 hours. The excretion of astatine was observed to be somewhat less than that of ^{131}I. The kidney[5] was the principal channel of elimination of ^{211}At as well as of ^{131}I.

Preliminary studies have been made with ^{211}At in the rat at lethal levels. Extensive functional injury to the thyroid gland in the rat was observed by determining the capacity of that organ to accumulate ^{131}I approximately one month after the administration of ^{211}At. In the thyroids of rats treated with ^{211}At there were observed histologically a few large and apparently relatively undamaged follicles. This circumstance presumably arose from the fact that the range of α-particles from ^{211}At is of the order of 70 μ whereas the β-particles of ^{131}I have a maximum range of 2000 μ. In this same series of experiments a thyroid gland was secured from a monkey which had received ^{211}At. In this instance the degree of injury to the thyroid gland was extreme and not one follicle could be seen on examination of serial sections. However, there were atypical cells present in the peritracheal region which showed[12] radioautographically the capacity to accumulate a tracer dose of ^{131}I. This observation of atypical cells in the peritracheal region, which were able to accumulate tracer amounts of radioiodine several

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months after the administration of destructive quantities of ^{131}I has been previously observed[6]. In the experiment employing monkeys, myxoedema was demonstrated in one animal which could be somewhat reversed by the oral administration of thyroid substance[5].

METHODS

The rats employed for both the ^{131}I and ^{211}At experiments were Sprague–Dawley females, 55 days of age and approximately 150 grammes in weight at the time the radiohalogen was administered by intravenous injection. The diet employed is similar to 'Diet 14' prepared by the University of California Institute of Experimental Biology[13]. The dose levels used for ^{131}I were 10, 30, 50 and 70 μc/g and there were 10, 18, 19 and 20 animals in each group respectively. The ^{131}I was essentially carrier-free and was obtained from the Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A. These animals were maintained for the first ten days in metabolism cages with no more than three rats in each cage and the cages were shielded from each other by ½-inch lead sheet. Space and facilities did not make it feasible to isolate each rat individually so that cross-irradiation from one animal to another would not occur. In addition some γ-irradiation was received by these animals from the excreta present in the metabolism cages. In a few instances, it was possible to sacrifice rats which were obviously not going to survive for more than a few hours. This made available gross and microscopic observations without disturbing the lethality determinations. At the end of the first week, the animals were weighed individually in order that changes in weight over an extended period of time could be observed. After ten days the animals were placed in stock cages in groups of five.

The preparation of ^{211}At has been described earlier[14]. ^{211}At was administered by intravenous injection at dose levels of 1·2, 1·4, 1·6 and 1·8 μc/g. The number of rats used in these experiments was 18, 30, 20 and 28 respectively. In this series of experiments the problem of cross-irradiation and radiation from excreta can be considered negligible in view of the character of radiations arising from ^{211}At. At the end of the first week the surviving animals were weighed and examined periodically. As with the ^{131}I experiments, animals which were about to die were sacrificed and the corresponding gross and microscopic pathological changes were observed. The tissues and organs removed for histological study in both the ^{131}I and ^{211}At studies included the thyroid gland, adrenals, pancreas, spleen, cervical and mesenteric lymph nodes, liver, lung and femur.

In order to evaluate adequately the mortality patterns in rats receiving both ^{131}I and ^{211}At, a probit analysis was made. Extrapolation was necessary to estimate the *MLD 60* (median lethal dose 60 days) values for both radiohalogens. The mathematical procedures employed were those described by D. J. FINNEY[15].

Two male rhesus monkeys weighing approximately 2·3 kg at an estimated age of six months were each given 0·42 μc/g of ^{211}At in February 1953. Two additional male monkeys of approximately the same age and weight were maintained as controls. Two female animals of very nearly the same age and weight received 0·8 μc/g of ^{211}At in May, 1953. As with the rats, the four monkeys that received astatine and the two controls were weighed

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periodically. Blood counts were taken every three to four weeks which included erythrocyte count, total white count, differential white count, and haemoglobin determination. A minimum of 500 cells were counted for each differential determination.

The results of this work and earlier studies with astatine indicated that it would be safe to employ this radiohalogen as a tracer in patients suffering from various disorders of the thyroid gland[8]. The main restriction was that the patients should be more than 35 years of age. In earlier experiments it was demonstrated that the accumulation of astatine by the thyroid gland of the rat following oral administration was nearly identical to the uptake observed following intravenous or intraperitoneal injection of this radiohalogen, when it was administered 18 hours prior to sacrifice of the animals[12]. The time factor in the clinical studies could not always be controlled as precisely as in animal work and ranged from 13·25 hours to 22 hours between the time of oral administration of 50 μc of ^{211}At to the patient and when the thyroid gland was extirpated. The entire specimen was weighed and a weighed fraction was left for routine hospital pathological studies. The remainder was brought to the Crocker Laboratory for assay. In each instance a small representative portion of the remaining tissue was taken for histological study. A separate file was maintained for each patient which included a brief history of the thyroid disorder, a gross description of the tissue obtained and the clinical diagnosis from the hospital pathologist. After gross examination of tissue specimen ^{211}At was isolated chemically by a modification of a technique employed earlier for the isolation of radioiodine from relatively large amounts of thyroid tissue[3, 16]. The accuracy of the chemical isolation of ^{211}At was checked by assaying the intact sample with a scintillating crystal γ counter which is sensitive to the 80 kV x-rays associated with the radioactive decay of astatine. No such check was possible for the specimens obtained from two patients that had previously received ^{131}I. In several cases both lobes of the thyroid were extirpated, and in one case, a specimen of cervical lymph node was obtained from a patient with papillary adenocarcinoma of the thyroid gland. Attention should be directed to the time consumed in the chemical isolation of astatine which may in some instances require more than six hours before the assay is completed.

RESULTS

The mortality curve for ^{131}I is shown in *Figure 1*. The *MLD 60* for ^{131}I was estimated to be 85 μc/g. It should be noted that the ordinate represents the probit of the per cent of mortality and the abscissa the logarithm of the administered ^{131}I.

Gross pathological changes observed in rats following the administration of ^{131}I are at present somewhat limited in scope, but enough animals have been seen so that several reasonably sound generalizations can be made. The animals dying during the first week showed very little except for somewhat swollen oedematous haemorrhagic thyroid glands. At no time was there any evidence of diarrhoea. During the second week after administration of ^{131}I there appeared grossly to be some moderate changes in some of the lymphatic tissues including the spleen and thymus but with relatively little reduction in their size. The thyroid glands were fibrous and greatly

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reduced in size. Occasionally haemorrhagic areas were noted in the lungs, but these were not extensive in either size or number. During the second and third weeks, the rats receiving 50 and 70 μc/g of ^{131}I developed a strange quacking sound associated with respiration which was presumed to be the result of injury to the larynx and vocal cords. A recording was made of this sound as compared to the normal squeaking a rat makes when slightly hurt. This record was then examined electrically with an oscilloscope. This procedure showed that the treated animals had a very marked change in sound pattern suggesting that the vocal cords may have been striking adjacent tissue which damped out part of the fundamental frequency. The animals that died during the second month following injection, grossly indicated very little except that there was no visible evidence of the thyroid gland. Two of the animals apparently died from suffocation, since it was apparent on autopsy that the trachea was almost completely obstructed.

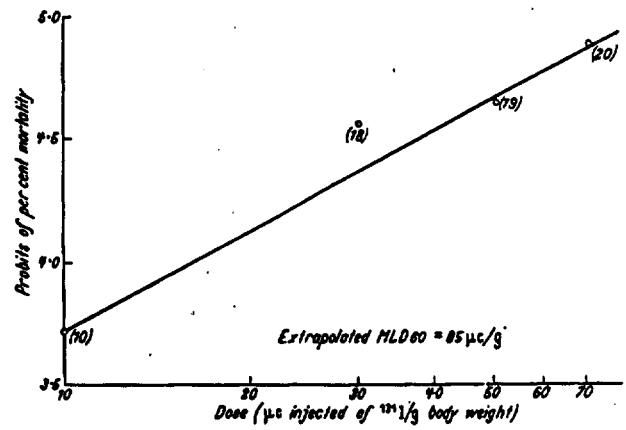

Figure 1. Probit analysis of 60-day mortality of Sprague–Dawley rats after a single intravenous injection of ^{131}I. The animals were females, 55 days old when injected. The number of rats at each dose level is indicated by numerals in parentheses beside the experimental points

The mortality curve of ^{211}At for 10 and 60 days is shown in *Figure 2*. The *MLD 60* is estimated to be 1·12 μc/g. The pattern of mortality in animals receiving ^{211}At was somewhat different from that found in animals given ^{131}I. During the initial week, there were relatively few deaths. A large wave of mortality occurred in the second week. As can be seen from *Figure 2*, the majority of the animals that survived the second week did not die during the subsequent fifty days. Grossly, the animals that died appeared to be much more severely affected. There was marked emaciation, oedema about the eyes, bleeding from the nose, and some diarrhoea. The animals usually showed pulmonary haemorrhage with large amounts of blood in the stomach and small intestines, much of which is presumed to have been swallowed blood from the lungs. The cervical and mesenteric lymph nodes usually were markedly haemorrhagic. The spleen showed from three- to eight-fold diminution in size, and after 14 days several spleens were seen in which there

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were several pale nodules approximately 1 mm in diameter. The pancreas, liver, kidney and ovaries were usually quite pale which probably arose from the fact that the animals had lost considerable blood. The thymus was very often so much reduced in size that it was difficult to isolate. The thyroid glands in animals dying during this time interval were usually small and frequently showed numerous small haemorrhagic areas. The lacrimal

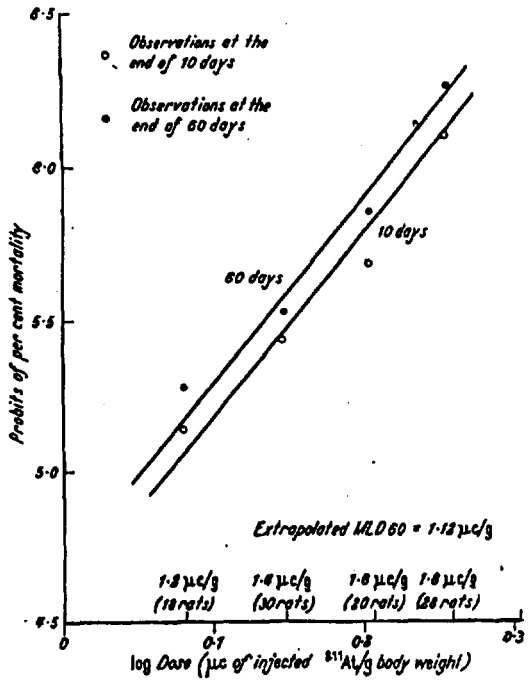

Figure 2. Probit analysis of the 10- and 60-day mortality of Sprague–Dawley rats after a single intravenous injection of ^{211}At. The animals used were females, 55 days old when injected. The number of rats in each group is indicated at the foot of the diagram

gland in several instances was found to be haemorrhagic. The adrenal glands were often haemorrhagic. Petechial haemorrhages were often seen in the fundus of the stomach, but not in the small intestines. Peyers patches appeared to have been completely obliterated. No gross changes were noted in any other organs. As yet limited information is available on the gross and microscopic changes in animals which died in the subsequent 50-day period following the administration of ^{211}At.

Microscopic changes were noted in the lymphatic tissues of animals treated with ^{131}I which indicate considerable injury to these structures. A photomicrograph of the spleen from an animal which was sacrificed at 7 days after the administration of ^{131}I is shown in *Figure 3*. For comparison, a

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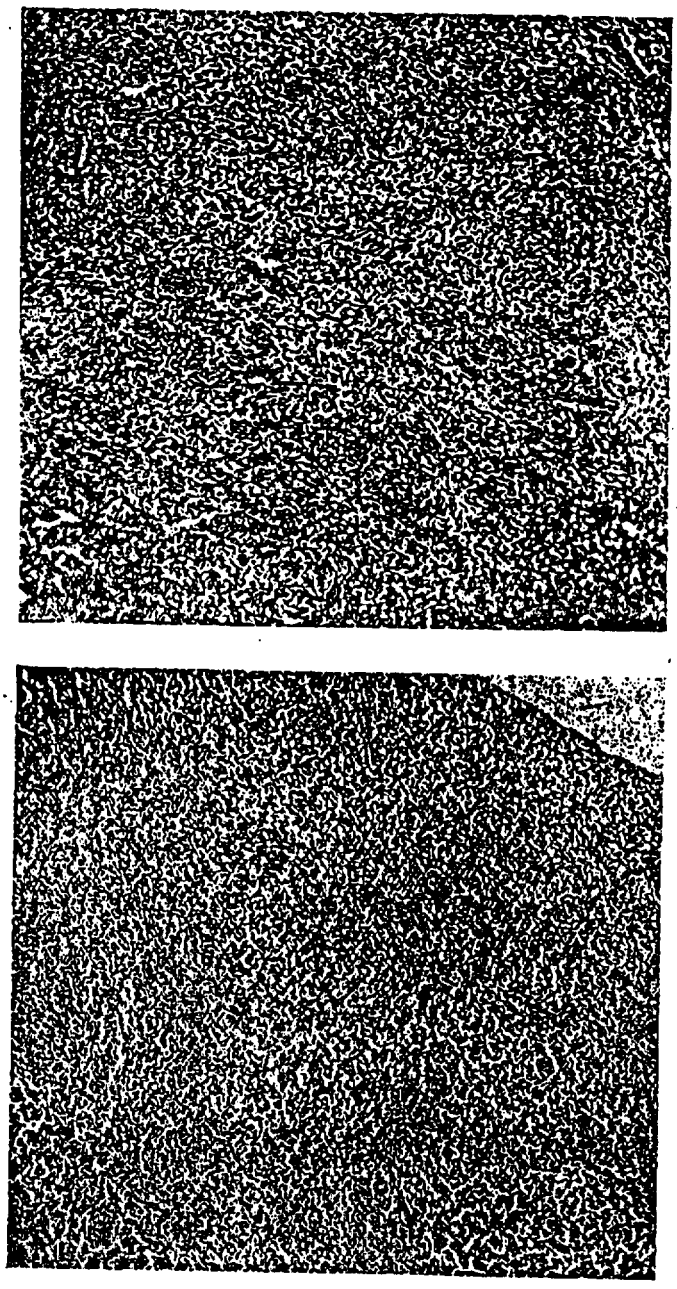

Figure 4. A section of spleen from a rat that had received 1·8 μc/g of ^{211}At and was sacrificed 6 days later. Here also may be noted the very marked injury and absence of Malpighian corpuscles. Stain: H and E. Magnification: × 55; reproduced without reduction

Figure 3. A section of spleen from a rat that had received 70 μc/g of ^{131}I and was sacrificed 8 days later. The marked degree of injury and loss of normal architecture may be seen. Stain: H and E. Magnification: × 55; reproduced without reduction

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section of an animal given ^{211}At and sacrificed at approximately the same time after administration of the radiohalogen is shown in *Figure 4*. A photomicrograph of the spleen of a control animal is shown in *Figure 5*.

From an earlier experiment rats receiving astatine in the range of 1 μc/g show at the end of a year, marked loss of hair, retardation of growth from the time of injection, and obviously are not healthy animals in that they do

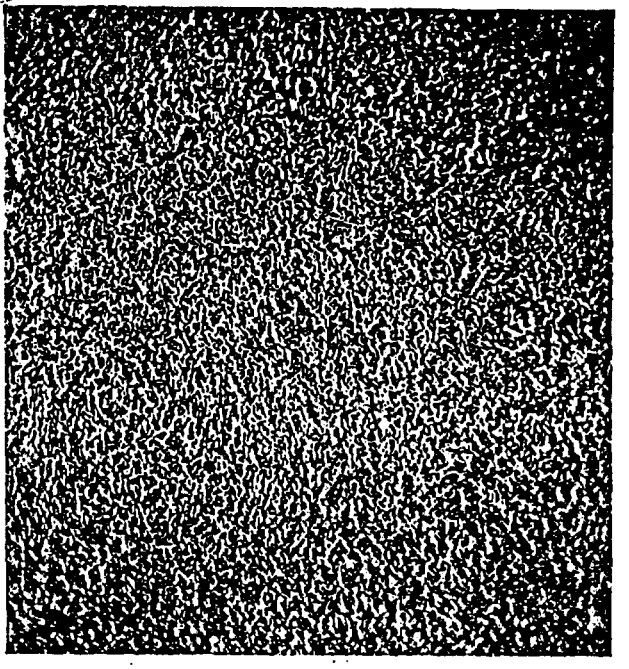

Figure 5. A section of spleen from a normal rat at the age of 65 days showing very clearly a Malpighian corpuscle. Stain: H and E. Magnification: × 55; reproduced with reduction

not maintain the normal degree of body cleanliness which is inherent in this particular strain of rat.

The monkeys likewise show similar changes including loss of hair, retardation of growth and apathy, all of which can be attributed to the diminished function of the thyroid gland. The haematological changes tabulated in *Table I* observed in the monkey suggest that there is some permanent injury to the haematopoietic tissue since there has been observed a permanent anaemia and leucopenia.

The human studies are summarized in *Table II*. Although the number of patients investigated is small, one striking observation was made. The accumulation of astatine by the thyroid gland in all but one of the patients is quite high, the range extended from 4·6 per cent to 17·8 per cent. The ratio of ^{131}I to ^{211}At accumulated in the thyroid gland of the rat for these

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time intervals is[5] approximately 10 to 1. A reasonable prediction of the ^{131}I accumulation in the thyroid glands of these patients would be in the range of from 12 to 30 per cent. Thus the selective accumulation of ^{211}At in the thyroid gland in this particular group of individuals appears to be significantly higher than would have been predicted from earlier work done with rats[5].

Table I. Effect of a Single Intraperitoneal Injection of Astatine-211 on Growth and Blood Picture of the Young Rhesus Monkey. The Monkeys were Six to Eight Months Old when Injected

Monkey	Sex	Days after injection	^{211}At dose	Body wt kg	RBC millions/mm³	WBC thousands/mm³	Haemoglobin g/100 ml	Differential white count	
								Lymphocytes	Granulocytes
3	M	358	Control	3·32	5·77	14·40	13·8	81·5	18·5
6	M	358	,,	3·92	7·27	9·25	15·8	92·0	8·0
2	M	358	0·42 μc/g	2·92	3·52	5·75	9·5	73·5	26·5
5	M	358	,,	2·89	3·53	3·30	11·2	85·0	15·0
1	F	294	0·83 μc/g	2·61	4·66	7·85	11·8	84·0	16·0
4	F	294	,,	3·35	3·56	7·05	10·3	68·0	32·0

Table II. Uptake of Orally Administered Astatine-211 by Human Thyroid Gland in Various Disorders of That Organ

Name	Age	Sex	Thyroid sample	Diagnosis	Time h	Per cent ^{211}At in sample	Conc. of ^{211}At %/g wet tissue
	40	F	Left lobe	Grossly normal	15	5·95	0·54
			Right lobe	,, ,,	18	11·85	1·19
			Cervical lymph node	Papillary adenocarcinoma	18	< 0·01	< 0·001
	41	F	Right lobe	Non-toxic metaplasia	13½	2·85	0·27
	31	F	Whole gland	Non-toxic nodular goitre with cyst formation	16½	6·75	0·55
	35	F	Whole gland	Toxic goitre (Lugolized)	15	6·66	0·21
	52	M	Right lobe	Graves' disease (Thyroxine, Lugolized)	18	0·172	0·017
	43	F	Left lobe	Non-toxic nodular goitre	14	6·55	0·26
	56	M	Left lobe	Grossly normal	13½	4·90	0·39
			Right lobe	Non-toxic nodular goitre	13½	2·56	0·024
	68	M	Whole gland	Non-toxic nodular goitre	22	4·61	0·021

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SURVEY OF THE RESEARCH

The acute injury and mortality pattern of ^{131}I in the rat is not easy to evaluate, since the ^{131}I is not uniformly distributed throughout the organs and tissues[6]. However, the general findings in the acute deaths resemble those seen following lethal doses of x-rays. The microscopic changes in the haematopoietic system, particularly the lymphoid tissues, were not as striking as had been anticipated.

The degree of injury to the vocal cords, larynx and adjacent structures was not anticipated. These findings are reasonable in view of the tremendous amount of irradiation to that area from the thyroid gland, since the range of the β-particles is sufficient to reach most of these regions. The subsequent severe occlusion of the trachea is a response that can also be attributed to the irradiation from the ^{131}I accumulated by the thyroid gland. An appropriate analysis for the mortality of the rat gives a preliminary estimation of the *MLD 60*, 85 μc/g, but many more rats must be given massive doses of ^{131}I in order to obtain reasonably accurate values.

A. GORBMAN states[8] that when mice weighing from 20 to 25 g were given ^{131}I in amounts greater than 400 μc, they usually died within a month. This would indicate that 20 μc/g of ^{131}I in mice was more than 50 per cent lethal in thirty days. In contrast, it was found in the experiments presented here that 85 μc/g of ^{131}I in rats produced approximately 50 per cent mortality in sixty days. Thus it would seem that rats are nearly four times less sensitive to ^{131}I than are mice. This differential effect may be due in part to the fact that the rat has a tendency to have a fuller digestive tract which will render the ^{131}I β-particles less effective in the irradiation of the gastro-intestinal tract because of self absorption.

The striking acute effect of lethal amounts of ^{211}At when given to the rat are difficult to interpret. The organs and tissues in which haemorrhage was most obvious upon both gross and microscopic examination include spleen, lymph nodes, lung, and adrenal. An earlier experiment[5] indicated that these four organs had the greatest relative selectivity for ^{211}At as compared to ^{131}I. The massive haemorrhage observed in these organs may have been due to increased capillary fragility.

The chronic changes in the survivors of lethal amounts of ^{211}At are even more difficult to interpret, because there are two independent actions of this radiohalogen. Most of the changes seen in the rat can be directly attributed to an endocrine imbalance due to the essentially complete ablation of the thyroid gland. The persistent anaemia and leucopenia very probably are due at least in part to the irradiation of the haematopoietic system. The chronic changes in the blood picture and general condition of the monkey are quite similar to those observed in the rat and here again one is faced with the problem of differentiating between the effects of the lack of thyroid hormone and the action of a relatively large amount of ionizing radiation given over a short period of time.

SUMMARY

(*1*) The acute and chronic effects of lethal amounts of ^{131}I and ^{211}At have been studied in the rat.

(*2*) A probit analysis for the mortality of ^{131}I and ^{211}At in the rat is presented.

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(*3*) The acute, gross and microscopic changes in ^{211}At in the rat have been observed in considerable detail.

(*4*) The chronic changes following administration of large amounts of ^{211}At in the rat have been investigated. There appear to be changes due to the absence of appreciable amounts of the thyroid hormone as well as radiation effects.

(*5*) Chronic changes have been observed in monkeys receiving ^{211}At. The effects appear to be related to both endocrine imbalance resulting from radiothyroidectomy and apparent radiation injury.

(*6*) A limited number of uptake studies of ^{211}At have been done with patients suffering from various disorders of the thyroid gland including carcinoma. There was no accumulation of ^{211}At in a metastatic carcinoma of the thyroid gland. The accumulation of ^{211}At in the thyroid gland in this series of patients appears to be relatively greater than was observed in the much larger number of rats[5].

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APPENDIX I

^{128}I decays with a half-life of 25 minutes, emits β-particles with a maximum energy of 2·02 MeV and a γ-ray energy of 0·428 MeV. ^{131}I decays with a half-life of 8·05 days with emission of β-rays most of which have a maximum energy of 0·608 MeV and an average energy of approximately 0·2 MeV. β-emission is followed by a complex cascade of γ-rays. The majority of these γ-rays has an average energy of 0·36 MeV[2].

APPENDIX II

There are two modes of decay for this radioisotope of astatine[8]. Forty per cent of the disintegrations with a half-life of 7·3 hours result in the emission of 5·86 MeV α-particles and the decay product is ^{207}Bi. This radioelement

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has a half-life of fifty years and decays by orbital electron capture accompanied by a complex series of γ-ray transitions to form stable ^{207}Pb. The remaining 60 per cent of the disintegrations of ^{211}At also have a half-life of 7·3 hours and decay by orbital electron capture to form ^{211}Po with the immediate emission of 80 keV polonium x-rays. Subsequently this radioisotope of polonium decays by the emission of 7·43 MeV α-particles with a half-life of 0·52 seconds to form stable ^{207}Pb.

REFERENCES

[1] HERTZ, S., ROBERTS, A. and EVANS, R. D. *Proc. Soc. exp. Biol., N.Y.* 38 (1938) 510.
[2] HOLLANDER, J. M., PERLMAN, I. and SEABORG, G. T. *Rev. mod. Phys.* 25 (1953) 469.
[3] HAMILTON, J. G. and SOLEY, M. H. *Amer. J. Physiol.* 127 (1939) 557.
[4] JOHNSON, H. W. and ALBERT, A. J. *Endocrinology* 48 (1951) 669.
[5] HAMILTON, J. G., ASLING, C. W., GARRISON, W. M. and SCOTT, K. G. *Univ. Calif. Publ. Pharm.* 2/2 (1953) 283.
[6] GORDMAN, A. *Trans. N.Y. Acad. Sci.*, Ser. 2, 11 (1949) 201.
[7] GOLDBERG, R. C., CHAIKOFF, I. L., LINDSAY, S. and FELLER, D. D. *Endocrinology* 46 (1950) 72.
[8] — — *ibid* 50 (1952) 115.
[9] CORSON, D. R., MACKENZIE, K. R. and SEGRÉ, E. *Phys. Rev.* 58 (1940) 672.
[10] JOHNSON, G. L., LEININGER, R. F. and SEGRÉ, E. *J. chem. Phys.* 17 (1949) 1.
[11] HAMILTON, J. G. and SOLEY, M. H. *Proc. nat. Acad. Sci., Wash.* 26 (1940) 483.
[12] — and DURBIN, P. W. Unpublished data.
[13] NELSON, M. *Univ. Calif. Inst. exp. Biol.* 'Diet 14'.
[14] GARRISON, W. M., GILE, J. D., MAXWELL, R. D. and HAMILTON, J. G. *Analyt. Chem.* 23 (1951) 204.
[15] FINNEY, D. J. *Probit Analysis*, 2nd ed. Cambridge University Press, London, 1952.
[16] HAMILTON, J. G., DURBIN, P. W. and GARRISON, W. M. Unpublished data.

DISCUSSION

A. H. W. ATEN, Jr (Amsterdam). Is it known whether any of the astatine taken up by the thyroid is bound in organic molecules? Attempts made in Amsterdam to incorporate astatine in simple organic molecules have been unsuccessful.

Answer. Attempts to isolate astatine homologues of the iodinated amino-acids including thyroxine have been fruitless. *In vitro* synthesis of the astatine homologue of iodo-benzene likewise met with failure. This is believed to be due to the chemically unstable properties of astatine which is known to possess at least five valence states most of which may be in rapid equilibrium with each other at the pH of body fluids.

J. ROTBLAT (London). Have any autoradiographic studies been made? The α-emission of astatine lends itself to high resolution track autoradiography, which should make it possible to obtain a detailed distribution of the astatine in the thyroid gland.

Answer. Autoradiographs have been made. Astatine seems to be present in the smaller follicles of greater histological activity. Dual autoradiographs with radioiodine and astatine were prepared. There were small follicles which took up a lot of radioiodine or a lot of astatine. In general, the larger follicles did not concentrate astatine.

E. E. POCHIN (London). Does thiouracil treatment increase the efficiency with which thyroid carcinomas concentrate astatine?

Answer. While propyl thiouracil enhances the accumulation of ^{211}At in the thyroid gland of the rat, no attempts have yet been made to investigate the effect of that drug upon the uptake of ^{211}At in carcinoma of the thyroid gland in experimental animals.

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Clinical data on uptake of ^{211}At in patients with thyroid disease

S. F. Lissitzky (Algiers). Some authors (Gorbman, Chaikoff) have observed the appearance of adenoma of the hypophysis after injection of large doses of radioactive iodine, and many weeks or months after. Did you observe such a phenomenon with astatine?

Answer. Neither neoplasms of the thyroid gland nor adenomas of the pituitary gland have been seen in rats receiving ^{211}At near the *MLD60* level at the end of one year.

W. V. Mayneord (London). Are your experiments likely to give any information on the relative biological effects when the same amount of energy is absorbed from alpha particles and beta particles in the thyroid?

Answer. There is a qualitative indication that the relative biological effectiveness of the alpha particles from ^{211}At in the thyroid gland of the rat may be greater than that of the beta particles of ^{131}I in that organ.

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