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THE ROLE OF CYCLOTRON IN MEDICAL RESEARCH

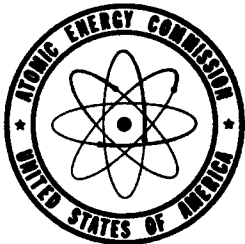
By  
Joseph G. Hamilton

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## THE ROLE OF CYCLOTRON IN MEDICAL RESEARCH

By Joseph G. Hamilton

The uses of radioactive isotopes in medical research can be conveniently divided into three principal categories; namely, the applications as tracers for the study of metabolic phenomena, as diagnostic aids in clinical medicine, and finally their role in therapy.

Frequently radioisotopes available from the chain-reacting pile do not have a sufficient degree of specific activity\* for satisfactory use. A number of radioisotopes which can be produced with high specific activity in the pile possess half-lives too short to be of any practical value. Then, there are a few cases in which the desired radioisotope may be made in the pile with high specific activity, but concomitantly there is formed another radioisotope of the same element whose half-life is of such duration as to render its use hazardous in man. Finally, there are several elements of biological and medical interest whose radioactive isotopes can be produced only by the cyclotron.

Rather than classifying the applications of the radioelements listed by subject, it is more convenient to present them here in the sequence with which they appear in the periodic table. Radioberyllium is of interest in view of the fact that beryllium and its compounds are serious toxicological problems in both industry and laboratories using this substance. During the past decade there have been observed ever-increasing numbers of individuals suffering from both chronic and acute pulmonary disturbances who have been exposed to beryllium. In a number of instances there has been a fatal outcome, and when careful survey of the individual cases was made it was found that there had been an exposure to either beryllium or one of its compounds. With laboratory animals it has been found possible to induce bone tumors following the parenteral administration of soluble beryllium compounds. There is considerable investigative work in progress with this element and its compounds, and in such studies cyclotron-produced radioberyllium has been found to be a valuable tool.

The very long half-life of  $C^{14}$  and the fact that a small but appreciable fraction finds its way to the skeleton to be retained there for long periods of time have discouraged the extensive use of this radioisotope in human studies and in particular when normal individuals might be employed. There is another radioisotope of carbon,  $C^{11}$ , with a half-life of 20 min, which can be produced only by the cyclotron. In a large proportion of biological and medical experiments employing radioisotopes, it is

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\*The term "specific activity" indicates the degree of radioactivity per unit weight of material.

possible to carry out the particular experiment over a period of from 5 to 6 half-lives of the radioelement being used. In the case of  $C^{11}$ , this signifies that any study using this substance is limited to a period of approximately 2 hr. Admittedly, this restricts its applicability to any but the simplest of experiments. To date, the only human studies of note have been those in which an attempt was made to ascertain whether in man the oxidation of carbon monoxide to carbon dioxide takes place in the body. This experiment, due to its relative simplicity in conception, made it possible to use  $C^{11}$ . The deuteron bombardment of boron oxide produces both radioactive carbon monoxide and carbon dioxide, and it is easy to rapidly effect a chemical separation of these two gases. The subjects then inhaled the labeled CO to which a few milliliters of stable CO had been added. Then at intervals up to 2 hr the subjects exhaled into solutions which entrapped the  $CO_2$  normally present in expired air. If any significant oxidation of the inhaled CO to  $CO_2$  took place, the  $CO_2$  fraction from the exhaled air would indicate the presence of radiocarbon. In these particular studies negative results were obtained. This implies that oxidation of CO to  $CO_2$  in man is probably not an important mechanism for the removal of CO from the body. Conceivably, there are other studies which could be made with this radioisotope of carbon such as the rate of exchange of bicarbonate ion in tissue fluids and related problems.

There is only one known radioisotope of fluorine which has a half-life of sufficient length to permit any biological and medical experiments. This radioisotope is  $F^{18}$  which has a half-life of 110 min and can be made only by the cyclotron. As yet, no studies in man have been made with this isotope, but it would appear that it might be applicable to short-term studies relating to the deposition of fluorine in the skeleton and in normal and carious teeth.

The three-year radioisotope of sodium,  $Na^{22}$ , is another example of a radioisotope which must be cyclotron produced. There is another radioisotope of sodium,  $Na^{24}$ , with a half-life of 14.8 hr, which can be made in large amounts by the chain-reacting pile. For most human tracer studies to date, the latter radioisotope has been employed. However, for certain long-term experiments such as the changes of the sodium space in normal individuals and patients suffering from various disturbance of water and salt balance,  $Na^{22}$  has been indispensable.

During War II, attention was drawn to the phenomena of the uptake and elimination of inert gases in man. The motivation for this was to attack the problem of the bends which occur in some individuals exposed to altitudes above 25,000 ft. This disease is due to the release of dissolved gases in the tissues and body fluids. The gas chiefly responsible for this effect is nitrogen since it does not undergo chemical combination in the body. Understandably, there are many modes of approach to this particular problem and one of them employed radioactive noble gases as tracers to determine their rate of accumulation and excretion in man under varying physiological conditions. The three radioelements employed were  $A^{37}$ ,  $Kr^{79}$ , and  $Xe^{127}$ . These gases were used rather than radionitrogen because the longest-lived radioisotope of nitrogen has a half-life of only 10 min. Also, it was desirable to compare the metabolism of the noble gases since

their coefficients of diffusion and solubility in water and fats vary. The first two can be produced in suitable amounts only by the cyclotron. In the case of xenon, the 5.3-day  $\text{Xe}^{133}$  is created by fission, but due to the fact that it emits a very soft gamma ray, its applicability was somewhat limited, making the cyclotron produced  $\text{Xe}^{127}$  a more useful tool. The results of studies with these noble gases brought forth the observation that the exchange in the body of gases which do not undergo chemical combination is not primarily determined by coefficients of diffusion or solubility, but by the quantity of blood passing through the tissues and organs. In other words, a structure such as muscle which has a relatively small blood flow per unit volume at rest picks up and discharges inert gases at a slower rate as compared to more vascular structures such as the liver and kidney. The rate of blood flow through a given organ or tissue can vary considerably under the influence of factors such as exercise, heat, cold, emotional tension, age, etc.

Potassium is one of the major mineral constituents of biological systems. In most vertebrates, including man, potassium is found largely within cells in contrast to sodium, most of which is present in the extracellular fluid. In man it has been shown that 30 per cent of all the potassium in red blood cells exchanges with the plasma potassium in 8 hr. A fertile field of study with radiopotassium is an investigation of the disturbances of potassium metabolism in diseases of the pituitary and adrenal glands. There are several neurological diseases which involve extensive alteration of the structure and function of the skeletal muscles. It is known that potassium metabolism is altered in several of these disease states. Radiopotassium would be a useful tool for the study of these disorders. It is possible to obtain radiopotassium from the pile but the radioisotope has a half-life of only 12.4 hr which restricts its usefulness. With the cyclotron another radioisotope of this element can be made by the transmutation of argon and has a half-life of 22.4 hr, which should be more useful in many instances. Also its specific activity is high which is desirable in some circumstances.

There are no satisfactory radioisotopes of manganese which can be produced in the chain-reacting pile. However, there are several that can be made in the cyclotron, notably  $\text{Mn}^{52}$  and  $\text{Mn}^{54}$ . As yet, no tracer studies in man have been done with soluble compounds of this radioelement.

Both the 57-day  $\text{Fe}^{59}$  and the 4-yr  $\text{Fe}^{55}$  can be made in the chain-reacting pile. However, two disadvantages appear with these radioelements when made in such a manner. In the first place the specific activity is frequently less than the experimenter would desire. Second, even when enriched  $\text{Fe}^{58}$  is prepared by the electromagnetic process, there is present with it an appreciable fraction of  $\text{Fe}^{54}$  with the result that when this separated material is bombarded with neutrons in the pile, there is concomitantly produced some  $\text{Fe}^{55}$ . Due to the fact that iron, once gaining entry into the body, is excreted very slowly, it does not appear desirable in most instances to permit the presence of appreciable amounts of  $\text{Fe}^{55}$  due to its long half-life and the possibility of subsequent induction of neoplastic changes. In the case of  $\text{Fe}^{59}$ , its half-life being 47 days, its use in man is justifiable if reasonable amounts are employed, and it can be produced in the cyclotron by

the transmutation of cobalt, and no  $\text{Fe}^{55}$  is formed. The tracer applications of radioiron have been most fruitful. Not only has a rather precise determination of the average survival period of the erythrocyte been established in man, which is of the order of 100 days, but the rates of red cell formation in normal subjects and patients with various disturbances of the blood-forming tissues have been studied. The use of these two radioisotopes of iron made possible the development of nutrient media for the transportation and storage of both whole blood and packed red cells for periods up to a month. This development took place during the War and was an important achievement from the practical aspect of the more effective treatment of War injuries by blood transfusions at the theaters of operation throughout the world. An ingenious experiment with  $\text{Fe}^{55}$  has demonstrated that the parasite of tertian malaria (Plasmodium vivax) selectively invades recently formed red blood cells.

For some time it has been known that cobalt is an essential element for animals, including man. Recently it has been found that an organometallic compound of cobalt, vitamin  $\text{B}_{12}$ , is very effective in the treatment of pernicious anemia. One of the amazing properties of this newly discovered vitamin is its potency. Patients with pernicious anemia can be kept free from the symptoms of this disease by the administration of as little as  $1 \mu\text{g}$  per day of  $\text{B}_{12}$ . Tracer studies with cobalt-labeled  $\text{B}_{12}$  would be of great interest. To accomplish this, it would be desirable to employ a radioisotope of cobalt with a very high specific activity and without too long a half-life. Pile-produced radiocobalt,  $\text{Co}^{60}$ , has a half-life of 5.3 yr and might be difficult to obtain with sufficiently high specific activity.  $\text{Co}^{58}$  has a half-life of 72 days and can be prepared by bombarding manganese in the cyclotron with alpha particles. It can be isolated with a very high specific activity.

The pile-produced radioisotope of copper,  $\text{Cu}^{64}$ , has a half-life of 12.8 hr which considerably limits its usefulness. There has been recently discovered a new radioisotope of copper,  $\text{Cu}^{67}$ , with a half-life of 56 hr which can be made only by the cyclotron and has a high specific activity. This extends the period of the experimental study to a considerable factor. While as yet biological and medical studies with radiocopper have been limited, it is certain that radiocopper will be found useful in the future, for copper is an essential element and plays a yet not clearly known role in the formation of red blood cells.

The 250-day radioisotope of zinc,  $\text{Zn}^{65}$ , can be made in the pile but only at a low level of specific activity. As this radioelement exists in but very small amounts in the body under normal circumstances, preparations of high specific activity are desirable. This can be accomplished by the deuteron transmutation of copper with the cyclotron.

The radioisotopes of arsenic made in the pile,  $\text{As}^{76}$  and  $\text{As}^{77}$ , have half-lives of but 26.8 and 40 hr, respectively, which restricts their applications, particularly if it is desired to study the metabolic properties of organic compounds of arsenic. There are two radioisotopes of arsenic which can be produced only by the cyclotron, notably  $\text{As}^{74}$  and  $\text{As}^{73}$  with half-lives of 19 and 90 days, respectively. During the War the 19-day radioisotope of arsenic was employed to investigate the distribution in the skin of human

subjects of the arsenic-containing war gas Lewisite. These radioisotopes of arsenic make the labeling of arsenical drugs feasible, thus rendering it possible to tag them in order to study their distribution and fate in the body.

Radiostrontium has been used in animals as a tool for the investigation of bone metabolism. The reason for employing this radioelement rather than a radioisotope of calcium arises from the facts that the only radioisotope of practical use has very soft radiations, rendering its measurement somewhat difficult, and it possesses a half-life of 180 days. It is particularly the long half-life that has discouraged investigators from administering radio-calcium to human subjects. It has been shown in animals that the metabolic pathways of strontium and calcium are almost identical, these two elements being in Group II of the Periodic Table, and possess chemical properties of great similarity. Thus, in most instances, radiostrontium can be effectively employed as a "stand-in" in the study of calcium metabolism. A radiograph and radioautograph of a slice from an amputated leg is shown in Fig. 1. The patient who had a bone tumor was given  $\text{Sr}^{89}$  before the amputation. The area of the tumor is indicated by the arrow and it can be seen that some  $\text{Sr}^{89}$  went into the tumor. The 53-day  $\text{Sr}^{89}$  can be prepared in the pile by two methods. Strontium element itself may be irradiated in the pile, but the radiostrontium formed by this procedure possesses such a poor specific activity that it is unsatisfactory to use as a tracer in most instances.  $\text{Sr}^{89}$  also appears as a by-product of nuclear fission. Unfortunately, a second radioisotope of strontium arises from fission,  $\text{Sr}^{90}$ , which has a half-life of 25 yr. Due to the presence of this long-lived radioisotope and the prolonged retention of strontium by the skeleton, it is inadvisable to employ fission-produced radiostrontium as a tracer in most human studies.  $\text{Sr}^{89}$  can be made in the cyclotron by the alpha particle transmutation of krypton, and it will have a high specific activity as well as being free from the 25-yr  $\text{Sr}^{90}$ . Another radioisotope of strontium which is produced only by the cyclotron,  $\text{Sr}^{85}$ , has a half-life of 65 days and is made by the deuteron transmutation of rubidium. In addition to the fact that it does not have an excessively long half-life, there are emitted penetrating gamma rays in the process of its disintegration. This presents an interesting opportunity to study the deposition in vivo of strontium in bone tumors and other pathological states where there is an abnormal deposition of calcium in the tissues. The in vivo technique requires no removal of tissues as the presence of the radioelement is determined by placing a Geiger counter over the surface of the body.

Large quantities of high-specific-activity radioiodine may be produced in the chain-reacting pile, and the most important of these radioisotopes is the 8-day  $\text{I}^{131}$  which is widely used in the study of iodine metabolism in normal individuals and patients suffering from various types of disorders of the thyroid gland. However, there is a radioisotope of iodine with a half-life of 56 days which can be produced only by the cyclotron. While, to date, this has not been used in medical research, its potential applications present some interesting possibilities. This longer-lived radioisotope of iodine makes it possible to study over a greater period of time the deposition and retention of iodine by the thyroid as well as its presence in other tissues and organs. Another interesting use for this material might be the labeling of the thyroid hormone, thyroxin, with both  $\text{I}^{131}$  and  $\text{I}^{125}$  in order to learn more about the manner by which the body metabolizes this hormone.

Element 85, which is the last of the series of halogens in Group VII of the Periodic Table, and which has been recently named astatine, does not exist in nature and can be made only by cyclotron bombardment. This element possesses the property of being accumulated by the thyroid to almost the same degree as has been observed with iodine. While the mode of its accumulation is as yet not clearly understood, it does appear that a study of its behavior in the thyroid may shed some additional light on the metabolic mechanisms responsible for the accumulation of iodine by the thyroid and its synthesis into the thyroid hormones. More important are its possible therapeutic applications which will be discussed later.

Among the list of cyclotron-produced radioisotopes discussed in the preceding paragraphs, to date,  $\text{Na}^{22}$  is the only one which can be said to have found diagnostic applications that may be considered to possess practical value to clinical medicine. As was stated in the sixth paragraph of this discussion this radioisotope has been employed in the study of sodium space and fluid balance in normal controls and in patients suffering from disturbances of sodium metabolism and water balance. These conditions arise most frequently in cardiac and renal disorders, and a measure of the efficacy of the therapeutic regimes employed can frequently be determined more satisfactorily by the use of  $\text{Na}^{22}$  as an indicator than by either the more conventional clinical methods or the 14.8-hr  $\text{Na}^{24}$ .

The use of radioisotopes in clinical therapy has to date been confined primarily to radioiodine in the treatment of hyperthyroidism and thyroid carcinoma and radiophosphorus for the therapy of the leukemias and polycythemia vera. A few therapeutic trials have been made with  $\text{Sr}^{89}$  for the treatment of bone tumors with not too encouraging results. However, it very well may be that the potential therapeutic applications of radiostrontium may not have been explored adequately to write off this radioelement as being of little or no therapeutic value. As has been pointed out in the preceding discussion, pile-produced radiostrontium would not be satisfactory if a therapeutic use of radiostrontium should be developed in the future.

Considerable work has been done on the use of radioactive colloids both in the treatment of the leukemias and the local therapy of a variety of malignancies. Among a number of radioelements employed for making radioactive colloids, cyclotron-produced radiomanganese is included in the group. However, it would not appear that radiomanganese colloids are superior to those available from pile-produced radioelements such as radiogold, radiocyttrium, etc. The 56-day radioiodine would not be a desirable therapeutic tool since it is preferable to use the shorter 8-day  $\text{I}^{131}$  radioisotope. Astatine, and in particular  $\text{At}^{211}$ , has a very intriguing nuclear property from the point of view of its potential use in the therapy of thyroid disorders. This radioisotope of element 85 decays by the emission of alpha particles. In the treatment of thyroid diseases, notably hyperthyroidism, by radiation, whether it be externally with X rays or internally as a result of the accumulation of radioiodine, there are varying degrees of irradiation of adjacent structures and normal thyroid tissue. With X rays it is obvious that one cannot aim the beam directly at the region to be treated without encompassing other organs and tissues to some degree within the field exposed, as well as radiating whatever normal thyroid tissue which may be present in the gland.

The situation is considerably better in radiiodine but even here the range of the more energetic beta particles of  $I^{131}$  is of the order of 2000 microns. The alpha particles of astatine have a range of approximately 60 microns which is only 5 or 6 cell diameters, thus a much higher degree of selective irradiation is hypothetically possible with this radioelement. Whether or not it will find its place in the therapeutic applications of radioisotopes in clinical medicine remains to be seen. The degree of selective destruction of the thyroid by astatine is shown in Figs. 2, 3, and 4.

Thus it is obvious that the cyclotron is a very useful tool for medical research. If one wishes to consider the aspects of investigative effort in all the life sciences, the value of this device becomes extended much further. It must be kept in mind that the chain-reacting pile and the cyclotron are in no sense competitive devices, but rather each has a role which it can uniquely perform. As sources of radioisotopes these two instruments complement one another. Throughout the country it is a frequent observation that, in those institutions which possess cyclotrons capable of preparing significant amounts of radioisotopes for biological and medical research, the investigative work in such areas leans heavily upon this type of source of supply even though there is a larger variety and quantity of radioisotopes available from the Oak Ridge National Laboratories. Figure 5 presents a photograph of the 20-Mev deuteron beam from the 60-in. cyclotron at the Crocker Laboratory. Table 1 lists a number of radioisotopes which either cannot be produced in the chain-reacting pile or are preferably made by the cyclotron for use in medical research.

Table 1--A Partial List of Cyclotron-produced Radioisotopes Which Either Have Been or May Be Expected to be Employed in Medical Research

Radioisotope	Nuclear reaction	Radiations	Half-life
Be <sup>7</sup>	Li <sup>6</sup> - p - n	$\gamma$	53d
C <sup>11</sup>	B <sup>11</sup> - d - 2n	$\beta^+$	20m
F <sup>18</sup>	O <sup>16</sup> - $\alpha$ - pn	$\beta^+$	112m
Na <sup>22</sup>	Mg <sup>24</sup> - d - $\alpha$	$\beta^+$ , $\gamma$	3y
A <sup>37*</sup>	Cl <sup>37</sup> - d - 2n	K, $\gamma$	34d
K <sup>42*</sup>	A <sup>40</sup> - $\alpha$ - pn	$\beta^-$ , $\gamma$	12.4h
K <sup>43</sup>	A <sup>40</sup> - $\alpha$ - p	$\beta^-$ , $\gamma$	22.4h
Mn <sup>54</sup>	Fe <sup>56</sup> - d - $\alpha$	K, $\gamma$	310d
Fe <sup>55*</sup>	Mn <sup>55</sup> - d - 2n	K	4y
Fe <sup>59*</sup>	Co <sup>59</sup> - d - 2p	$\beta^-$ , $\gamma$	47d
Co <sup>58</sup>	Mn <sup>55</sup> - $\alpha$ - n	K, $\beta^+$ , $\gamma$	72d
Cu <sup>64</sup>	Zn <sup>64</sup> - d - 2p	K, $\beta^-$ , $\beta^+$ , $\gamma$	12.8h
Cu <sup>67</sup>	Zn <sup>67</sup> - d - 2p	$\beta^-$	56h
Zn <sup>65*</sup>	Cu <sup>65</sup> - d - 2n	$\beta^+$ , $e^-$ , $\gamma$	250d
As <sup>74</sup>	Ge <sup>74</sup> - d - 2n	$\beta^-$ , $\beta^+$ , $\gamma$	19d
As <sup>73</sup>	Ge <sup>72</sup> - d - n	K, $e^-$	90d
Kr <sup>79*</sup>	Br - d - 2n	K, $\beta^+$ , $\gamma$	34h
Sr <sup>85</sup>	Rb <sup>85</sup> - d - 2n	K, $\gamma$	65d
Sr <sup>89*</sup>	Kr <sup>86</sup> - $\alpha$ - n	$\beta^-$	53d
I <sup>125</sup>	Te <sup>125</sup> - d - 2n	K	56d
Xe <sup>127*</sup>	I <sup>127</sup> - d - 2n	$e^-$ , $\gamma$	34d
At <sup>211</sup>	Be - $\alpha$ - 2n	K, $\alpha$	7.5h

\*Can be made in chain-reacting pile.

p--Proton, d--Deuteron, n--Neutron,  $\alpha$ --Alpha particles,  $\beta^-$ --Negative beta particles (negatron),  $\beta^+$ --Positive beta particles (positron),  $\gamma$ --Gamma rays, K--Orbital electron capture (associated with emission of K and L X-rays of the element formed by this mode of decay),  $e^-$ --Internal-conversion electrons

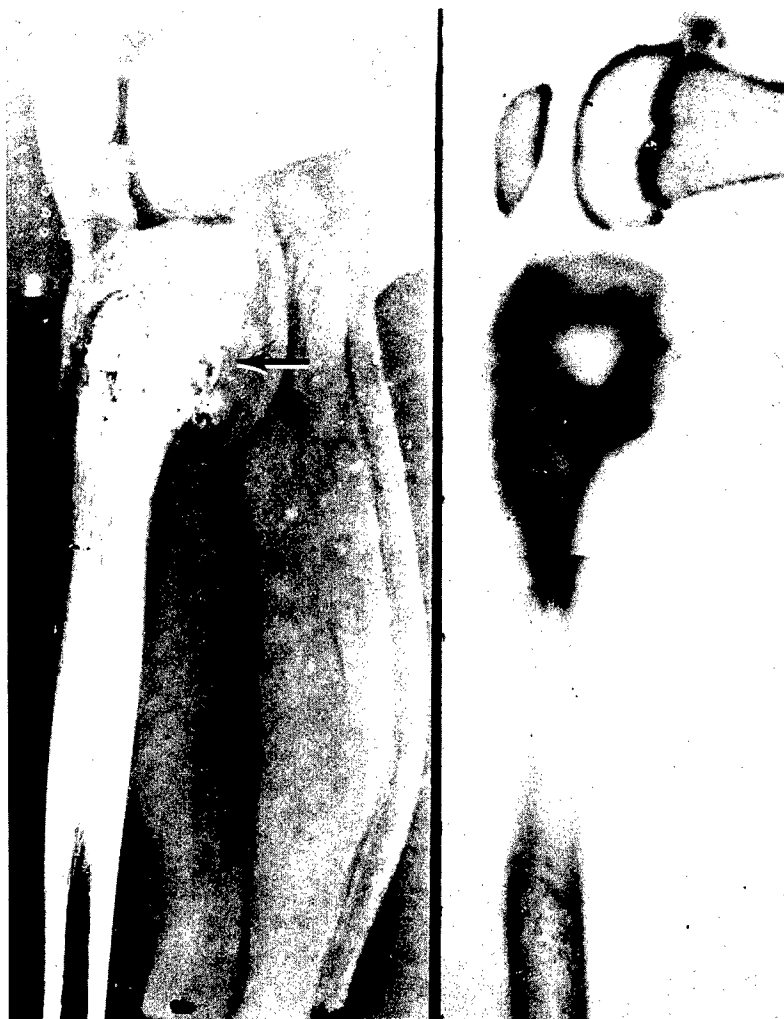


Fig. 1--Roentgenogram and corresponding strontium radioautograph of a thick section of an amputated leg from a patient with osteogenic sarcoma. The region of the tumor, indicated by an arrow on the roentgenogram, has extended out into the surrounding soft tissue. The radioautograph demonstrates that there was considerable deposition of radiostrontium in the region of the tumor, some concentration in the normal bone, notably the epiphyseal line, and relatively little present in the soft tissue.

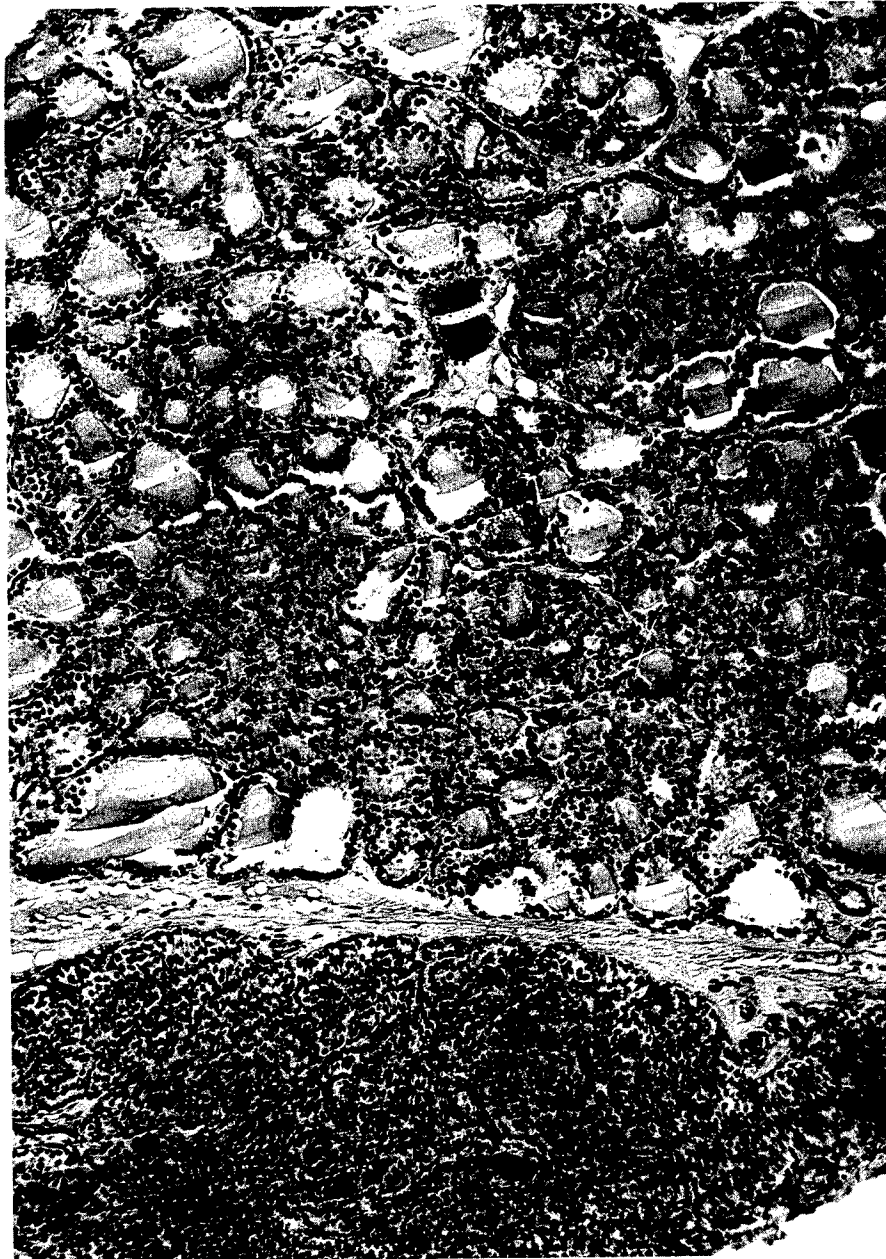


Fig. 2--Normal thyroid and parathyroid tissue of the rat. The parathyroid tissue is the dense cellular mass at the bottom of the photomicrograph.

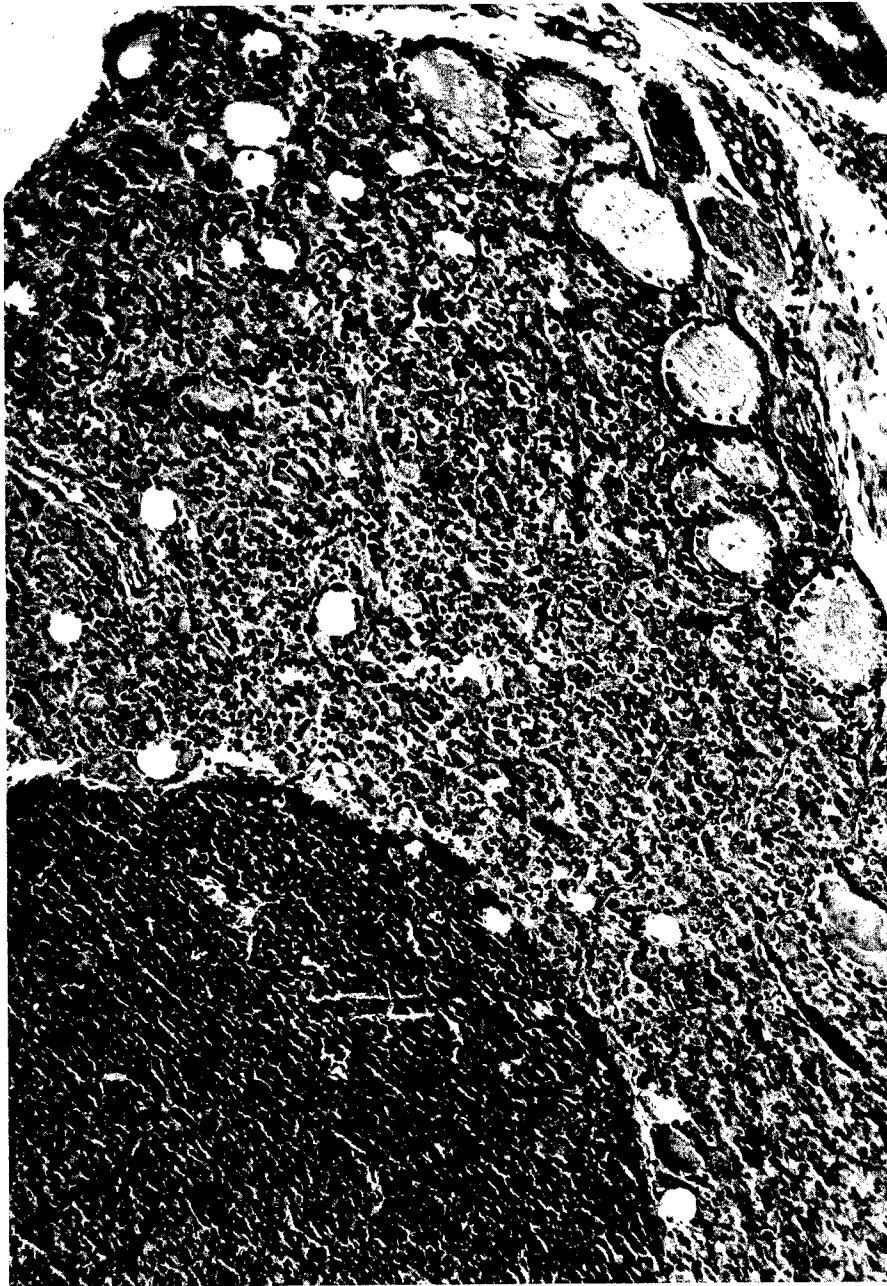


Fig. 3--The changes produced 41 days after the administration of  $41 \mu\text{c}$  of  $\text{At}^{211}$ . Note that only the periphery of the thyroid shows any normal looking tissue. The parathyroid appears undamaged.

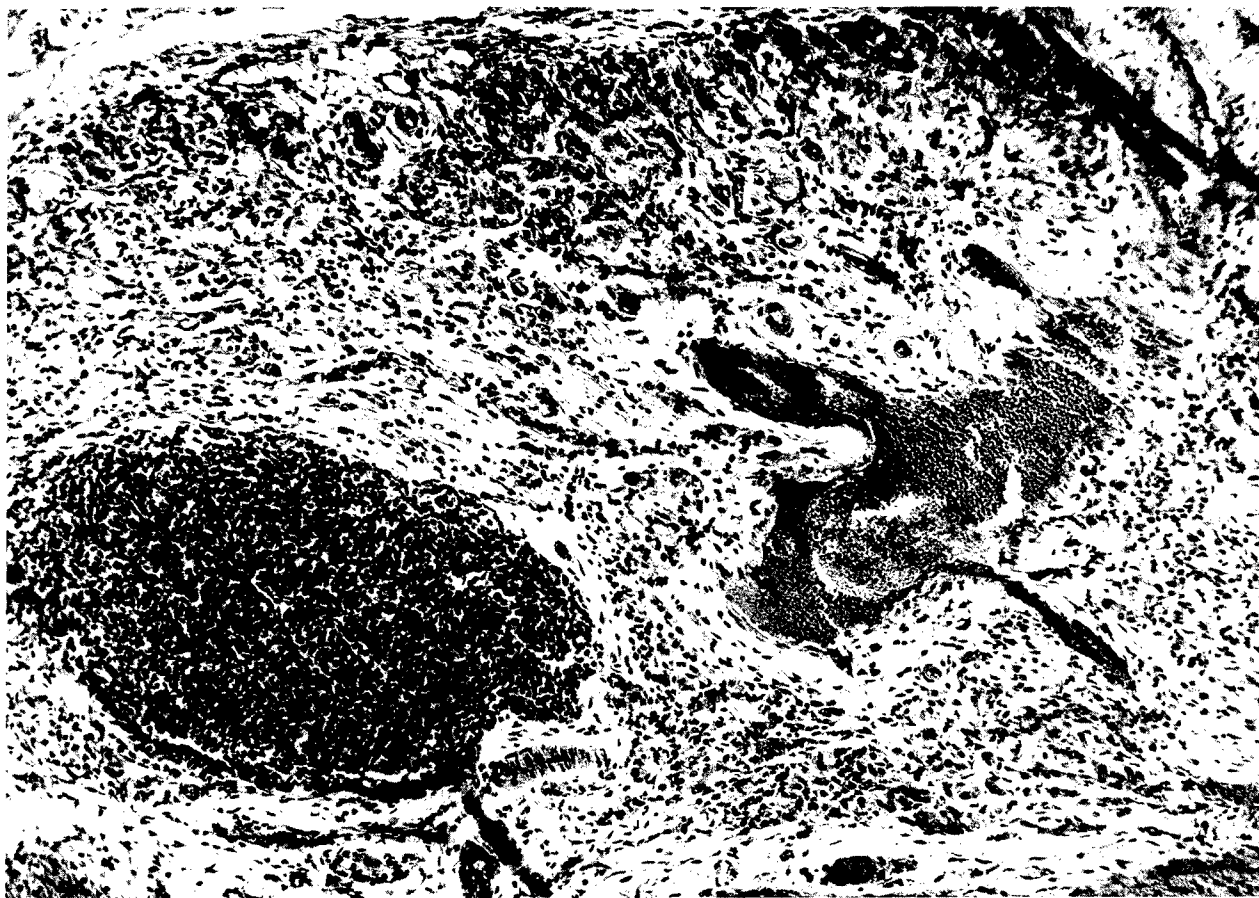


Fig. 4--The effect of 80  $\mu\text{c}$  of  $\text{At}^{211}$ , after 41 days. No recognizable thyroid tissue remains, and the parathyroid shows no evidence of radiation injury.

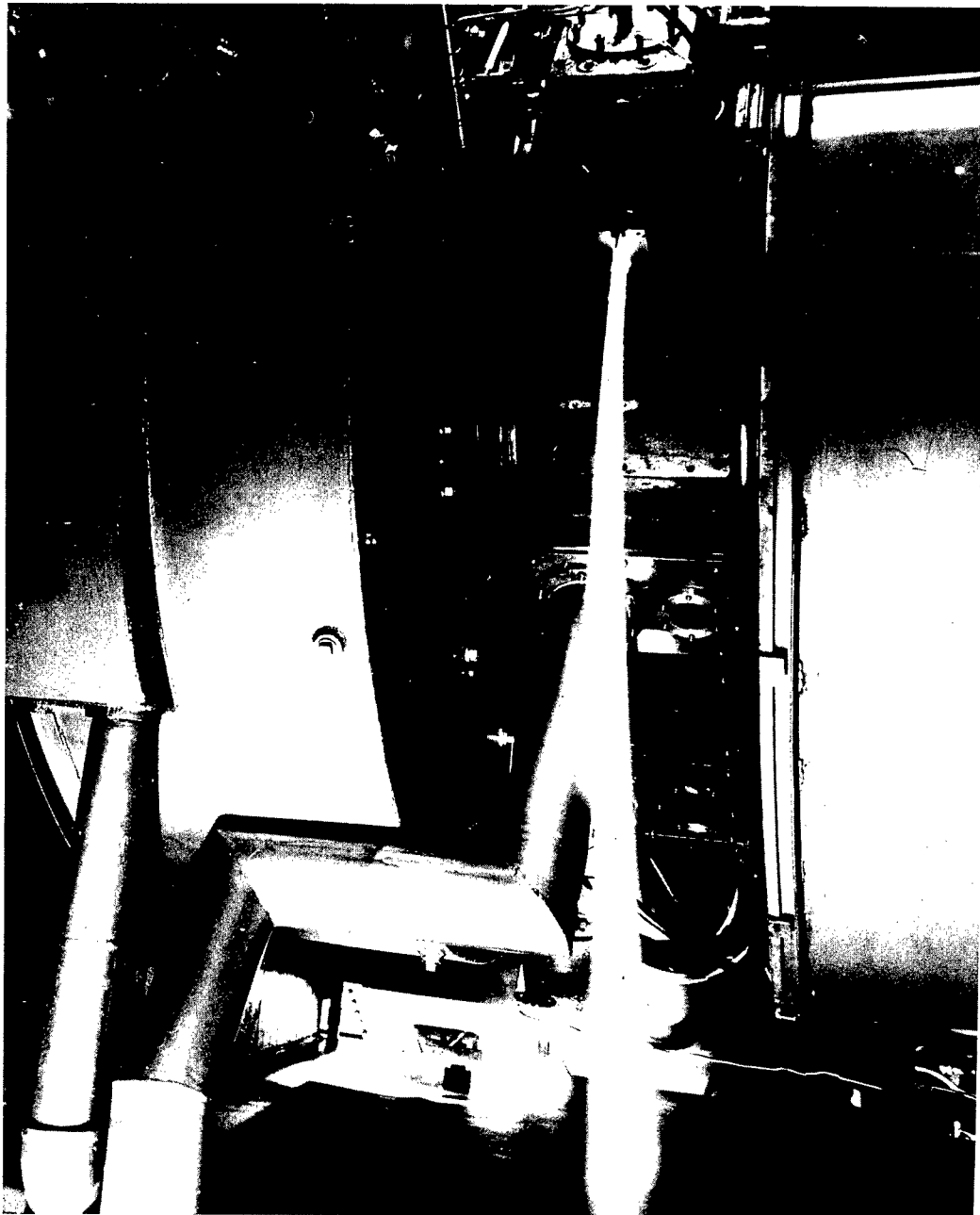


Fig. 5 — A 20-million-volt deuterium beam from the 60-in. medical cyclotron in the Crocker Laboratory. The beam is about 2 m in length, and the end of it is striking the solid steel frame of the magnet which weighs about 200 tons. This machine was designed and built by Professor E. O. Lawrence and his associates in 1938.

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