ACROMEGALY

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Acromegaly was first described in 1886 by Pierre Marie.[1] His description is based on two cases of his own and on five that he obtained from the literature dating back to 1722. He did not relate the syndrome to a primary disturbance of the pituitary but rather to a general nutritional disease. Later he regarded acromegaly as the result of subnormal functioning of the hypophysis. For a long time, acromegaly was assumed to result from hypersecretion of the growth hormone. Only lately, however, have investigators been able to demonstrate by immunochemical methods an increase in the titer of growth hormone in the serum of these patients.[2, 3]

For many years, patients with acromegaly have been treated by hypophyseal X irradiation and, in some cases, by surgery.[4] More recently, large doses of estrogens have been employed.[5] Dr. Peter Bishop of Guy's Hospital, in evaluating his large series of patients with acromegaly, has pointed out that about 50 per cent of these die before the age of 50.[6]

My introduction to the study of acromegaly came while I was an interne under Harvey Cushing at the Brigham Hospital. To us, acromegaly seemed a common enough disease because there were always eight or ten patients in the hospital undergoing treatment. Later, as Resident in Medicine for Dr. Francis G. Blake, I was assigned to assist in the care of Dr. Cushing while he was a patient in the New Haven Hospital. During Dr. Cushing's convalescence in the hospital, he arranged to have several patients with acromegaly or Cushing's disease admitted for study,[7] and I became further interested in the disease and in treating it by irradiation of the pituitary gland. We carried out a series of experiments in which we irradiated the pituitary gland of rats[8] and learned quickly that with the doses delivered, we did not appreciably influence the rate of growth or cause classic histologic destructive changes in the gland. This was because we were not able to irradiate selectively the gland and there was danger of excessive radiation to such surrounding structures as the hypothalamus and the cranial nerves. Nevertheless, since those days, patients with such pituitary tumors as those associated with acromegaly, Cushing's disease and chromophobe adenoma have continued to be treated with X radiation, particularly if there is no involvement of the optic chiasm. Certainly this form of therapy has real value, but with the low doses used (2000–3000 rad and at most

4000 rad in 3 to 4 weeks) the end results have not been satisfactory with reference to life expectancy.

During those years when I was associated with Dr. Cushing, he became very much interested in nuclear physics and began to collect many of the earlier writings of some of the great physicists such as Ernest R. Rutherford, J. J. Thompson, and C. T. R. Wilson of cloud chamber fame. Dr. Cushing's collection, one of the best on early nuclear physics, is now in the Yale Medical Library. Frequently in the course of our conversations, Dr. Cushing would say to me, "This field of isotopes and radiations in nuclear physics is going to be exceedingly important to biology and medicine in the future. It reminds me of the development of bacteriology when I was a young doctor." He urged me to go into this field, especially since some of my studies already involved radiation.[9] As a medical student and later as an interne and resident, I was often visited by my brother, Ernest O. Lawrence, then an assistant professor of physics at the University of California. I can remember especially one of his visits to Boston. With a German physicist, Professor Otto Stern, who was teaching in Boston, we had dinner in an Italian restaurant. My brother made a drawing on the tablecloth, sketching his idea for a new atom smasher he later called a "cyclotron." This device would be a way to get very high voltages, using low voltages, by whirling atoms within a circle instead of accelerating them in a linear fashion. Professor Stern said, "Ernest! Sie müssen sofort nach California zuruchgehen und nach seiner Vorstellung arbeiten müssen. Das hört sich gut an." The next day my brother took the train back to California and soon had his first small cyclotron in operation.

In 1935 I became actively engaged with my brother in the early experiments with radioactive isotopes and some of the new radiations produced in one of the first cyclotrons.[10, 11, 12, 13, 14] Some of the beams and particles from the various accelerators and cyclotrons had interesting biological and medical implications and applications.

Figure 1 is a Wilson Cloud Chamber picture of what heavy particle ionization in tissue might look like when compared with ionization from X radiation. We soon found that these densely ionizing particles were several times more destructive to tissue than equal amounts of roentgen or gamma rays.[10] In more recent years we have obtained even heavier and more penetrating particles, which have other quite unique characteristics from the medical standpoint.[15, 16, 17] And now, during the past seven years, we have been using the beam clinically. A brief report of some of the results in the treatment of patients with acromegaly follows.[18]

Figures 2 and 3 show the setup for exposure of the pituitary in the sella turcica. The beam of alpha particles enters through the patient's temple, the patient's head being enclosed in a tight-fitting plastic mask.

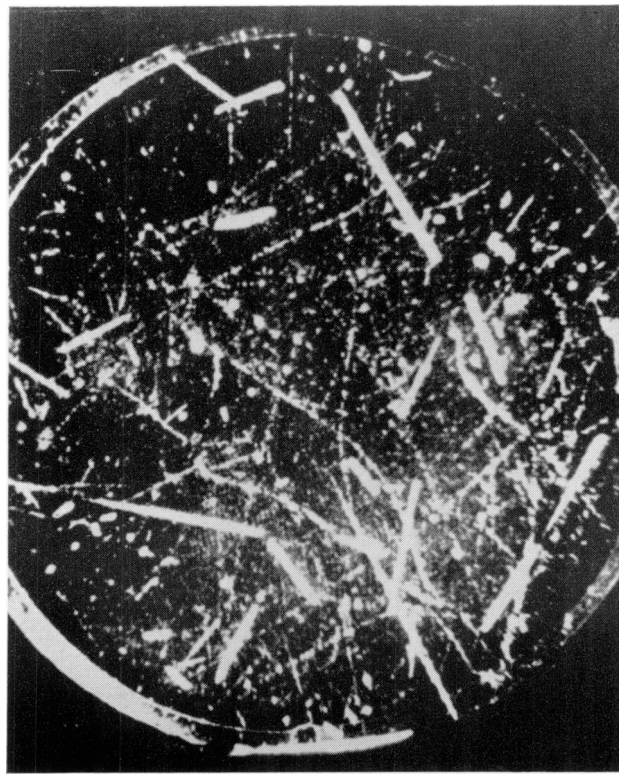

FIG. 1. Photograph of proton (thick tracks) and electron (thin tracks) ionization in Wilson Cloud Chamber while receiving neutron and gamma irradiation from cyclotron.

AP and lateral roentgen films are made to align and center the beam on the sella. During exposure, the patient's head is rotated to an angle of 35° to the right and to the left and through 12 fields by angling the table through 6 increments to the right and 6 to the left.

Figure 4 shows the dose distribution in the three axes as per cent of maximum dose to the center of the pituitary against distance from the center. It also permits comparison of 900-MEV particles and 2-MEV X rays. Especially in the X axis, but also in all axes, there is relatively greater dosage to the vital tissues when 2-MEV X rays are used. This is particularly a problem in the case of the Z axis where the optic and other cranial nerves and temporal lobes receive relatively large doses of radiation.

Seventeen patients with active acromegaly have been treated during the past 4 years. Usually six exposures were given at 2-day intervals. Table 1 gives the pituitary irradiation doses and postirradiation survival

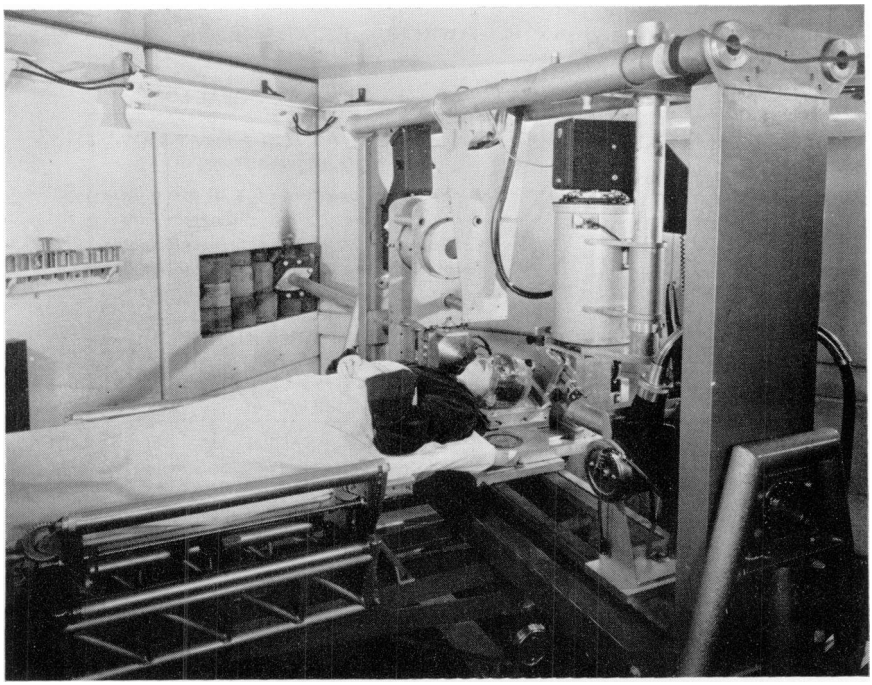

FIG. 2. Patient in position for pituitary irradiation.

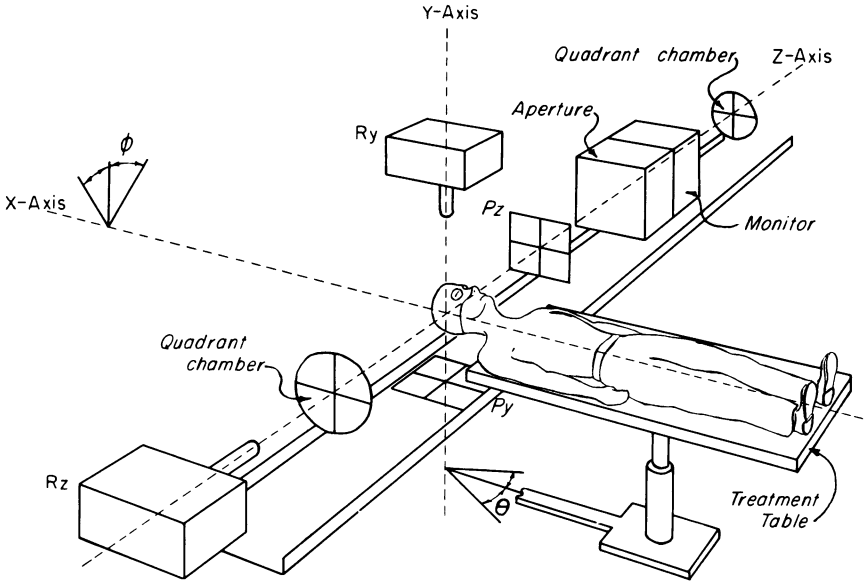

FIG. 3. Diagram illustrating irradiation axes.

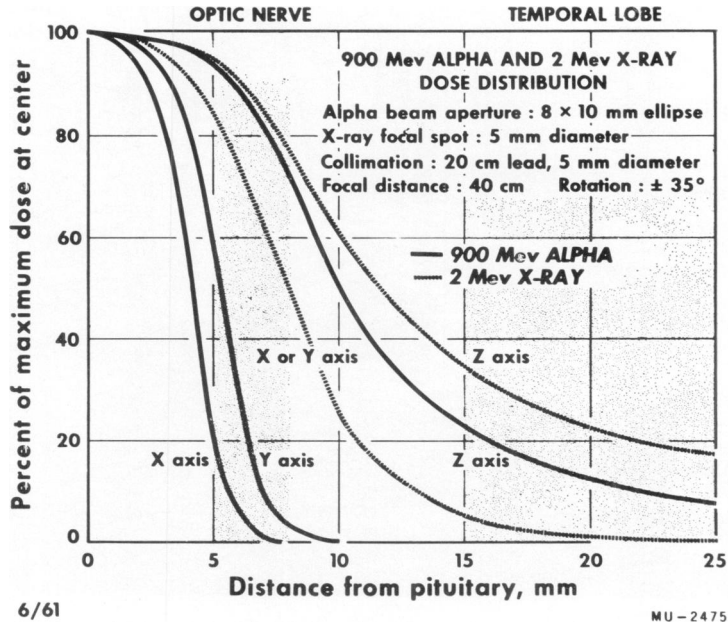

FIG. 4. Doses of radiation at various distances from center of sella when using 900 mev alpha particles and 2 mev X rays (calculated).

times for these patients. Clinical and metabolic studies on these patients before and after pituitary irradiation were carried out. Table 2 summarizes the laboratory findings* and Table 3 the changes in symptoms following treatment.** Sixteen patients are still living. All but one are known to be feeling well and have resumed their normal work. One patient has signs suggesting temporal lobe invasion and exploration may be necessary. One patient with long-standing acromegaly died of cardiomegaly and a coronary occlusion 3½ years after treatment.

* As a group the male acromegalic patients also had high urinary estrogens.

** Three acromegaly patients with a concurrent diagnosis of diabetes mellitus controlled with insulin or DBI prior to irradiation were controlled subsequently with diet alone. Four patients (non-diabetic) had abnormal glucose tolerance curves prior to irradiation which improved subsequently, 2 becoming completely normal. One patient with a normal curve prior to therapy had an abnormal curve 2 months later which has remained abnormal for over 2½ years.

Two patients had visual field defects when seen initially. One had surgery for decompression just prior to irradiation, but vision in his right eye has remained poor. The other, who had questionable visual field defect prior to therapy, showed no evidence of abnormality 9 months later. Another patient, who had right lateral strabismus, showed definite improvement in oculomotor capacity following therapy.

TABLE 1

Pituitary Irradiation Data and Survival Times for 17 Acromegaly Patients

Patient	Irradiation		Survival, Months After Irradiation
	Rad	Days	
LAG	4000*	21	43 (*Deceased*)
BAL	4500†	19	43
FOL	7200	12	41
REE	7200	12	40
WAD	7200	12	40
ODL	5880*	12	38
SEG	7200	11	38
KNE	5170	11	26
BRN	7200	11	22
TRT	4400*	11	22
ZUP	4000*	11	21
JON	9000	11	21
BUT	4200	11	19
HUN	4500*	11	18
BRL	4000	11	15
VIL	4000	18	10
LON	6000	12	1

* Received prior X-ray therapy, over 4000 r

† Suprasellar portion of tumor excised

Note: Survival data compiled January 1962

TABLE 2

Laboratory Findings

	Average Value Before Treatment	Average Value After Treatment
Total estrogen (μg/24 hr)	30.4	15.1
17-ketosteroids (mg/24 hr)	15.9	10.1
20,21-ketols (mg/24 hr)	17.8	14.4
I^{131} uptake (% at 24 hr)	14.7	18.5
Serum phosphorus (mg/100 ml)	4.7	4.2

TABLE 3

Changes in Symptoms

Symptom	Number of Patients With Symptom Before Treatment	Changes After Pituitary Irradiation			
		Improved	No change	Worse	No evaluation
Acral enlargement	16	11	4	0	1
Changes in facial appearance	16	5	10	0	1
Tongue enlargement	15	3	11	0	1
Headache	15	11	2	1	1
Lethargy and weakness	14	9	4	0	1
Excessive perspiration	13	9	3	0	1

FIG. 5. Photograph of patient with severe exophthalmos.

FIG. 6. Photograph of patient shown in Figure 5 two years after treatment with 10,000 rad of alpha particles.

With this particulate radiation, it seems that we may be able to deliver as much as 10,000 to 15,000 rad to the sella region* and, pending the development of hormonal or chemical means of control, such total energy may lead ultimately to much better control of the symptoms and signs of acromegaly and to further extension of life.

Figures 5 and 6 show a patient with severe exophthalmos before, and two years after, treatment with 10,000 rad to the sella. This is another condition now under study and treatment using the beam.[19,20,21]

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* In the treatment of brain tumors and soft tissue tumors, the Bragg curve is used and an even better relation between the depth dose and the dose to normal tissue and skin is achieved [15, 19, 20, 21].

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DISCUSSION

DR. GRANT W. LIDDLE (Nashville): I was delighted to learn that mountain climbers and drinkers of soda pop were capable of making significant contributions to physics, because I have been impressed with the fact that significant advances in endocrinology are frequently brought about by people who are not themselves primarily endocrinologists. I think that we have observed an example of that in the studies Dr. Lawrence has presented here today.

It seems to me that there are three objectives in the treatment of acromegaly. The first is to arrest the growth of the tumor, the second is to correct the metabolic abnormality, and the third is to accomplish the first two objectives without creating further abnormalities.

The tumor growth can almost always be arrested by conventional doses of radiation; but contrary to the textbooks, the metabolic abnormality is frequently not corrected by conventional doses of radiation. We have several patients who have continued to exhibit "smoldering" acromegaly after receiving maximum tolerable doses of conventional radiation.

Dr. Lawrence, I think some people have the impression that with your techniques it is possible to localize the radiation so well that it might be possible to re-treat some patients who have already received as much brain irradiation as they can tolerate. Is this true, or is it important that you have an opportunity to treat the patient from the beginning?

DR. LAWRENCE (Closing): Thank you, Dr. Liddle.

With reference to patients for treatment: I think we prefer to have patients who have not previously received X radiation or gamma radiation, because usually the fields employed have been so large that, with the average pituitary dose of about 4000 rad over a three- or four-week period, the dose to the surrounding brain tissue is such that the tolerance of normal brain tissue has been approached. We are giving somewhat larger doses because of our more selective radiation, but because it is known that delayed brain damage may occur as late as four or five years after irradiation, we must wait another year or two before we can exceed the present dosage schedule of 6000 to 7000 rad over a period of two weeks. It is my belief that eventually we will be able to deliver at least 12,000 rad over a two-week period to the pituitary glands of these patients without damaging surrounding nervous structures.

I would urge you as internists to ask your radiologist colleagues to use rotating techniques for the delivery of radiation to the pituitary, because in this way irradiation of the cranial nerves and brain is somewhat minimized. Even though alpha particles or protons are not now widely available, the use of rotating techniques with X rays from a 2-million or similar voltage machine, and small fields, makes possible the delivery of relatively larger doses to the pituitary, and it is conceivable that much better control of acromegaly will result.