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April 1963

HEAVY PARTICLES, THE BRUGG CURVE AND THE SUPPRESSION
OF PITUITARY FUNCTION IN DIABETIC RETINOPATHY*

By

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Diabetes mellitus is a condition treated with much success since the introduction of insulin and later of the oral anti-diabetic drugs. However, normal life expectancy has not yet been achieved, largely due to vascular disease. Diabetic retinopathy, a serious complication often associated with varying degrees of other vascular complications, leads to impairment of vision and often blindness. Other than careful control of the blood sugar during the course of the diabetes, no adequate preventative measures have been found. The relation of the pituitary to diabetes (1) and the reports of the disappearance of diabetic retinopathy in patients developing spontaneous hypopituitarism (2,3) have suggested the

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*** We have had the advice, assistance, cooperation and consultation of many physicians in the care of these patients, but we are especially appreciative of that given by Dr. Peter Forsham, Dr. Frederick Cordes, Dr. Samuel Kimura, Dr. Michael Hogan and Dr. Vincent DiRaimondi. We also wish to recognize the important contribution to the work of our associates Dr. Franco Sangalli and Dr. Richard Carlson who are still associated with the work in a consultation capacity.

possible importance therapeutically of pituitary ablation or the suppression of pituitary function. Some favorable results have been achieved after complete or partial hypophysectomy (4,5,6,7,8).

In 1935 we found a relatively greater biologic effect of heavy-particle-induced tissue ionization (proton) on both normal and neoplastic tissue in a series of experiments with the 37-inch and 60-inch cyclotrons (9,10,11). On the basis of these experiments therapeutic trials were made with these relatively low-energy neutrons (12,13). In more recent years, heavy charged-particles with higher and higher energies have become available, so that tissue ionization with a high relative biological effect is available (14) and associated with minimal scatter and great depth dose due to the Bragg curve (15). Thus, with comparatively little intervening radiation dose, energy can be delivered in relatively localized packages to great depths in tissue (16).

In clinical studies during the past ten years (17,18,19) it has been found that with the teletherapeutic delivery of high-energy heavy ions such as protons, alpha particles or deuterons to the sella turcica in fractionated doses, it is possible to inhibit the function of or to destroy the pituitary gland in patients suffering from breast cancer, diabetic retinopathy and various other conditions in addition to the use of these ions in treating tumors directly (8,20), and in the production of localized lesions in the soft tissues or nervous system of animals and man (16,21,22,23,24).

Our investigations in patients suffering from advanced diabetic retinopathy began over five years ago. We used positively-charged "heavy particles" which at the end of their track in tissue produce

much denser ionization than that following X radiation. Sometimes we use this Bragg curve to localize the dense ionization at the depths to destroy or inhibit the function of the pituitary, but more commonly we have used a head-rotation technique to localize radiation. Metabolic studies in a group of irradiated patients show a gradual fall in the values of target-organ hormones controlled by the pituitary; the curves resemble those seen in patients following surgical hypophysectomy (See Figure 1).

We have used the heavy particle beam to achieve partial or complete hypophysectomy in an attempt to slow down the progressive, severe diabetic retinopathy in 71 patients. The earlier group of diabetic patients were given amounts of radiation sufficient to produce complete suppression of pituitary function. Most of these patients had a prompt fall in insulin requirements and subsequently required replacement therapy with hydrocortisone and thyroid. Because of concern over the possibility of a greater susceptibility to radiation damage in the diabetics with generalized, and in most instances advanced, vascular disease, it was decided to treat the later patients with less radiation in order to reduce the risk to the structures adjacent to the pituitary, e.g. the extraocular motor nerves and the temporal lobes. Such a change in dosimetry made it possible to observe the effects of suppressive pituitary irradiation, and also to study some patients with less advanced retinopathy who were relatively free from other major diabetic vascular complications. Most of the patients, 54, received 8,000 to 14,000 rads in 11 days. While most of the patients in this

group showed some gradual fall in their end-organ function (see Figure 1) the majority of these patients have not required replacement therapy. In this group better evidence of suppression of pituitary function is shown in a plot of the daily insulin requirements as shown in Figure 2. The group treated with 10,000 - 11,000 rad showed a marked fall in insulin requirement while those receiving less radiation showed less change. Paralleling this decrease in insulin requirement we have observed in many of these patients improvement in vision, and such objective improvements in appearance of the eyegrounds as decreases in the frequency of the hemorrhages, microaneurysms, revascularizations and exudates.

All of the patients in this report were referred for pituitary irradiation by their private physicians. In most cases, they had been cared for by medical physicians as well as an ophthalmologist, and were considered to have progressive retinopathy. Each patient received a detailed ophthalmological examination by at least two ophthalmologists as well as our medical staff prior to irradiation. In addition, retinal photographs were taken before and periodically after treatment.

Within the group of 71 patients there were 46 males and 25 females. Median age at time of irradiation was 37 yrs (range 21 to 65 yrs). The diagnosis of diabetes mellitus was made in 61 patients prior to age 40, the median age being 18 yrs (range 1 to 40 yrs); the median age for the remaining 10 patients was 54 yrs (range 43 to 60 yrs). Median duration of the diabetes prior to pituitary irradiation was 16 yrs (range 1 to 31 yrs), and that of the retinopathy was 2 yrs (range from less than 1 yr to 14 yrs).

Of the 60 patients still living, 24 were treated over 18 months ago, the longest survival time being 5 years post-irradiation. Eleven patients have died, and the median survival time of these deceased patients is 16 months (range 4 to 33 months). All eleven patients had moderate or advanced nephropathy and/or cardiovascular involvement prior to irradiation. Six patients died in uremia and 3 of acute myocardial infarction. One patient died suddenly in a local hospital while visiting away from home. A postmortem was not performed, but he was thought to have had a cardiac death. Another patient with advanced diabetic neuropathy has postural hypotension which became increasingly severe following radiation. He also became markedly insulin sensitive, and he died 14 months after treatment in another hospital. Terminally he became comatose and died in cardiovascular collapse. Hypoglycemia and adrenal insufficiency were probably contributory causes to his death. Three of the above patients developed permanent extraculomotor palsies (received doses above 20,000 rad). Neuropathological examination in those patients where postmortem examinations were performed revealed other changes which were not symptomatic and recognized prior to death. Neuropathological studies are being completed and will be reported separately (25). No radiation side effects have been observed in any of the surviving patients. One patient had severe insulin reactions during which he developed a partial right hemiparesis. Although the hemiparesis has improved sufficiently for him to return to work, he still has residual neurological damage. All the patients are alerted to the increased insulin sensitivity that occurs following pituitary irradiation, and their physicians

have been advised to administer hydrocortisone during periods of stress.

Changes in retinopathy post-irradiation have been evaluated in 61 patients (10 patients were treated too recently for follow-up evaluation). In 38 of these the retinopathy had stabilized, while in 23 patients it had progressed. Patients who had small recurrent pre-retinal hemorrhages were classified as progressive regardless of the magnitude of the hemorrhage and its effect on their visual acuity. In a number of these cases they appeared to have had fewer hemorrhages after treatment than before. This might indicate that irreversible damage was present in some vessels and pituitary suppression did not affect these vessels, although it may have benefited others. Of the 38 patients showing stabilization, 14 have also shown improvement in vision. In these patients there was definite improvement in visual acuity as well as subjective improvement. We take retinal color photographs before and periodically after treatment in all cases for evaluation of results. In a recent analysis we found that when there is improvement in vision there is also improvement in the retinal photographs. Figures 3 and 4 show the types of changes in the retinopathy that have been observed in two diabetic patients following pituitary irradiation. The retinal photographs in Figure 3 are those of patient H.W. whose case history will be described in the text (see case 6). Figure 4 shows retinal photographs of a recently treated patient R.F., a 57-year-old attorney who had known diabetes for 10 years and retinopathy for approximately one year. He had only taken insulin since the development of retinopathy. He had mild diabetic neuropathy, but

no clinical cardiovascular or renal disease.

Tables 1, 2 and 3 summarize the clinical data for the 61 patients for whom we now have follow-up information. The patients are grouped according to the duration of their follow-up. In addition there follow detailed summaries of six of our patients in order to illustrate some of the important clinical features which we have observed.

CASE SUMMARIES

Case 1. M.C., a 37 year old white housewife was the first diabetic patient treated. Diabetes mellitus was diagnosed in 1944 at age 23. She was started on 35 units of insulin daily and was satisfactorily controlled with only occasional mild insulin reactions. Eye symptoms first occurred in October 1957 when she noted blurred vision in her right eye and was told that she had a retinal hemorrhage. In January 1958 she had a retinal hemorrhage in the left eye and a diagnosis of advanced bilateral diabetic retinopathy was made.

When she was first seen in February 1958 the fundus in the right eye could not be visualized because of massive vitreous hemorrhage and a posterior subcapsular cataract; visual acuity was 20/100. In the left eye there were extensive neovascularization and numerous microaneurysms. In addition there were a number of areas of retinitis proliferans. The macula was obscured by numerous folds in the retina which appeared to be secondary to edema and traction. The visual acuity in the left eye was 20/40. She had a reduced creatinine clearance, but no other evidence of nephropathy or cardiovascular disease. Insulin dosage was 45 units daily.

Heavy-particle radiation was administered to the pituitary gland in 7 treatments over a 14-day interval. Therapy was completed March 24, 1958.

Subsequently her daily insulin requirement fell, dropping from 45 to 20 units in four months, and remaining at this level for almost two years. In April 1960, because of increased insulin reactions, the dosage was further reduced to 5 units daily. However, in May 1960 replacement therapy with hydrocortisone (10 mg b.i.d.) and thyroid (1-1/2 gr daily) was started and her insulin requirement increased to 10 units daily. In December 1962 she was taking 6 units of insulin daily and was relatively free of major insulin reactions.

Funduscopy examination two months after irradiation again revealed the cataract in the right eye, and it was felt that the left eye had stabilized and may have been a little improved. Fifteen months post-irradiation vision in the right eye had improved so that the patient could count fingers; the left eye remained stabilized. After 22 months of stability the patient suffered a severe hemorrhage in the left eye. There was gradual improvement in the vision of this eye, but in May 1960 it was felt that there was slight, but definite, progression of the hemorrhagic and exudative lesions of the left eye. By February 1961, almost 3 years after irradiation, her diabetic retinopathy showed signs of improvement since the previous examination. Visual acuities were: right eye, 20/400 with posterior capsular cataract; left eye, 20/70 with posterior peripheral cortical cataract. Four years after irradiation her visual acuities were 20/200 on the right and 20/30 on the left.

When last seen in December 1962 her visual status was unchanged and there had been no further hemorrhages.

Case 2, L.F., a 39 year old white physician was 13 years old when diabetes mellitus was diagnosed. He was reasonably well controlled with insulin diet, having infrequent insulin reactions and no episodes of diabetic coma. In 1954 the patient was told that his right eye showed signs of diabetic retinopathy, but blurred vision was not noted until 1955. Since that time there had been progressive loss of vision in his right eye with frequent bouts of sudden blurring of vision. There had been small hemorrhages in the left eye, also. Diabetic neuropathy involving the left oculomotor nerve was diagnosed in August 1958 when diplopia developed.

When we first saw this patient in October 1958 the right eye showed diabetic retinopathy with severe retinitis proliferans and detachment of the retina. Visual acuity was extremely poor. The left eye showed early diabetic retinopathy with some venous dilatation and a few microaneurysms; visual acuity was 20/20 with correction. There was no serious renal involvement or cardiovascular disease. His insulin dosage was 48 units daily.

Heavy-particle radiation was administered to the pituitary gland in 8 treatments over a 17-day interval. Therapy was completed November 17, 1958.

Following therapy his daily insulin requirement decreased, dropping from 48 to 36 units in five months, and by one year post-irradiation was 30 units daily. In February 1960 he complained of fatigue and was started on thyroid (1/2 gr. daily) with improvement

in this symptom. However, extreme fatigue and decreased libido developed in December 1960 and he was then started on prednisolone (5 mg per day) and testosterone; his insulin requirement remained at 30 units. The insulin requirement in October 1961 was 28 units. In August 1962 (almost 4 years post-irradiation) he was taking 25 to 30 units of insulin daily and continuing the replacement therapy.

Retinopathy was stabilized during the first year postirradiation; there were no obvious retinal hemorrhages and there was a questionable decrease in the number of microaneurysms. During the second year minimal progression of his retinopathy was reported; visual acuities were 20/40 with the right eye and 20/20 with the left eye. In March 1962 (almost 3-1/2 years post-irradiation) the right eye still showed the retinal separation but the diabetic process appeared inactive. The left eye had some vascular abnormalities but was generally improved. Visual acuities were: right eye 20/100; left eye 20/20. At 4 years post-irradiation stabilization of retinopathy continues.

Case 3. J.E. This 24 year old white housewife was 11-1/2 years old when diabetes mellitus was diagnosed. She was treated with a diabetic diet and insulin in doses up to 110 units daily without achieving good control. Ocular symptoms began in June 1956 when she suddenly developed vitreous hemorrhage in the right eye and a diagnosis of diabetic retinopathy was made. During the second of two pregnancies in 1958, both of which terminated spontaneously, she developed edema of the legs, abdomen and face which persisted and was controlled by diuretic therapy.

In April 1959 fundusopic examination of the right eye revealed

extensive neovascularization extending from and obscuring the disc. The vascular pattern was distinctive in that it remained proximal to the retina and did not extend into the vitreous. There were punctate hemorrhages in the region of the right macula and the foveal reflex was absent. The visual acuity in this eye was 20/50. The left eye had a similar type of retinopathy, and visual acuity was 20/40. In addition to diabetic retinopathy the patient had mild nephropathy (creatinine clearance was 40 cc per minute; proteinuria was 1+). There was no obvious cardiovascular disease. Her pre-irradiation insulin dosage was 35 units daily.

Heavy-particle radiation was administered to the pituitary gland in 6 treatments over an 11-day interval. Therapy was completed April 24, 1959.

Following therapy her insulin requirement fell from 25 to 10 units daily in four months. Recurrent furuncles interfered with her diabetic control, however, and her requirement fluctuated. Cortisone replacement therapy was initiated in August 1959 and her insulin requirement then increased to 20 to 30 units daily. It was noted in September 1959 that the patient had not menstruated since therapy in April. Her pituitary gonadotropins were still negative at 5 mouse units, F.S.I. was 3.2 $\mu\text{g}/100\text{ ml}$, and the patient was started on thyroid and estrogen. In November withdrawal bleeding occurred after stopping estrogen therapy for two weeks. In May 1960 it was noted that her insulin requirement varied from 15 to 30 units daily. In March 1961 she underwent surgery for a pilonidal cyst with multiple sinuses and her cutaneous infections

subsided following this surgery. Diabetic control was somewhat improved.

Her retinopathy was thought to be improved in September 1959 in that the neovascularization of the discs and microaneurysms were less pronounced. At one year post-irradiation the retinopathy remained markedly improved, and when the eyes were examined in June 1961 (over 2 years post-irradiation) this stabilization had continued and visual acuities were 20/30 bilaterally.

Her diabetes was further complicated by repeated cerebral vascular accidents. In November 1959 there was slight ptosis of her left eye lid which was thought to be due to minimal radiation damage to the left oculomotor nerve. In September 1960 she was hospitalized with a bizarre behavior pattern. Evaluation at that time showed that in addition to clear-cut emotional disturbances, the patient had definite features of diffuse organic mental disease. In January 1961 she experienced sudden onset of weakness of the right side with slurring of speech and was hospitalized with right-sided paralysis. Neurologic examination showed findings consistent with a thrombotic occlusion of a branch of the left middle cerebral artery. During the next year she had several more strokes and gradually deteriorated. The patient expired February 7, 1962 (33 months post-irradiation) in uremia. Post-mortem examination of the cerebral vessels showed an area of complete occlusion of the left middle cerebral artery and multiple infarcts of the brain.

Case 4. D.D., a 33 year old white grocery clerk was 17 years old when diabetes mellitus was diagnosed. Insulin therapy was initiated and he was fairly well controlled and had no episodes

of diabetic coma, although he had many insulin reactions including several severe reactions which resulted in coma. Early in 1957 he was told that he had diabetic retinopathy, and a few months later he first noted blurring of vision. In March 1958, while hospitalized for an episode of atrial tachycardia, a diagnosis of progressive retinopathy was made. Heparin therapy was started in August 1958. In November 1958 he had a hemorrhage in his right eye, and in March 1959 a hemorrhage in the left eye.

In September 1959 the right eye had a diffusely hazy vitreous due to hemorrhage. There was extensive retinitis proliferans extending anteriorly into the vitreous and attaching to the temporal and nasal portions of the retina. Fine details could not be ascertained, but in the peripheral portion there were patches of white exudate and occasional hemorrhages. Visual acuity was finger counting at 2 feet. The left eye was also hazy due to recent vitreous hemorrhage. There were mounds of exudate and occasional hemorrhages in the temporal retina. The nasal retina was obscured by a large band of fibrous tissue. Visual acuity in this eye was finger counting at 5 feet. Other vascular complications were advanced nephropathy and hypertensive cardiovascular disease. Mild neuropathy was also present, and the patient had been impotent for several months. He was taking 35 units of insulin daily.

Heavy-particle radiation was administered to the pituitary gland in 6 treatments over an 11-day interval. Therapy was completed November 20, 1959.

His daily insulin requirement dropped from 35 to 30 units in

3 months and remained at this level for over a year and then dropped to between 25 and 30 units. There was some decrease in the adrenal steroid excretion and fall in PEI, but no replacement therapy was required.

At 3-1/2 months post-irradiation there were no new retinal hemorrhages and he reported subjective improvement in his vision. In September 1960 retinopathy remained stabilized. The vitreous was clearer and retinal detail was more readily delineated than on the pre-irradiation examination. His visual acuities were somewhat improved: right eye 3/200; left eye 10/200. By June 1961 he could read newsprint and recognize people at a distance. In January 1962 the appearance remained unchanged and his visual acuities were further improved (right eye 20/100; left eye, 20/50). He had had no further hemorrhages.

In July 1961 his cardiovascular disease became further complicated when he suffered a cerebral vascular accident with resultant left hemiparesis. This gradually improved. In April 1962, however, he had another cerebral vascular accident from which he did not completely recover. The patient expired August 19, 1962 (33 months post-irradiation) in uremia.

Case 5 S.R., a 22 year old white male student was 5 years old when diabetes mellitus was diagnosed. Insulin therapy was initiated and his dose varied from 10 to 80 units daily. He had an average of 4 to 5 insulin reactions per year and 4 episodes of ketosis and acidosis, but no diabetic coma. In January 1960 he noted failing vision in the left eye and examination showed essentially no vision in this eye due to diabetic retinopathy. In May 1960

he had another large hemorrhage in the left eye and developed secondary glaucoma. Because of severe, uncontrollable pain this ultimately required treatment with retrobulbar injection of alcohol. When we first saw him in June 1960 the left eye was functionless. In the fundus of the right eye there was marked distortion of the normal architecture with large areas of hemorrhage in the region of the disc. The veins were markedly dilated and irregular. There were numerous microaneurysms and areas of neovascularization. The whole retina appeared edematous. In addition he had advanced nephropathy and hypertensive cardiovascular disease. His pre-irradiation insulin requirement was 50 units daily.

Heavy-particle radiation was administered to the pituitary gland in 6 treatments over a 13-day interval. Therapy was completed July 18, 1960.

His insulin dosage did not change following therapy, although it was felt that he was becoming insulin sensitive. He had no other evidence of hypophysectomy and did not require replacement therapy.

In September 1960 there was definite improvement in the vision of his right eye. However, in December 1960 he noted failing vision in this eye, and in January 1961 developed secondary glaucoma in this eye. He was then essentially blind.

In April 1961 he experienced a sharp, somewhat diffuse, substernal pain. When hospitalized here in May 1961 he suffered nausea, vomiting, fever, tachycardia and severe chest pain. He was in cardiac failure and was treated with supportive measures for an acute anteroseptal myocardial infarct. He expired May 4, 1961.

(9 months post-irradiation) and post mortem findings showed extensive infarction of the left ventricle.

Case 6 H.W., a 21 year old white rancher was 3-1/2 years old when diabetes mellitus was diagnosed. Insulin therapy was initiated and he had good control with diet and insulin, taking as much as 80 units per day. In 1944 he was told that he had fundus changes with small hemorrhages, but he had no visual symptoms until October 1960 when he noted blurred vision in his left eye. Vision in this eye slowly deteriorated.

In April 1961 his retinopathy was characterized by marked irregularity and dilatation of the retinal veins. There were numerous microaneurysms and punctate hemorrhages distributed throughout both optic fundi, particularly in the peripheral portions. In addition there were a few inconspicuous exudates. The discs and other areas of the fundi showed moderate neovascularization. He could read newsprint with difficulty with his left eye, and the vision in his right eye was not grossly impaired. There was no clinical evidence of nephropathy or cardiovascular disease. His pre-irradiation insulin dosage was 60 units per day.

Heavy particle radiation was administered to the pituitary gland in 6 treatments over an 11-day interval. Therapy was completed May 19, 1961.

His daily insulin requirement declined from 60 to 55 units during the first five months post-irradiation, but he had rather frequent insulin reactions. In January 1962 he increased his insulin to 60 units again, but he was having minor reactions and the dosage was reduced to 50 units and maintained at this level

through September 1962.

His retinopathy remained stable during the first 5 months and his visual acuities were: right eye, 20/25; left eye 20/40. During the next few months he had two episodes of minor retinal hemorrhages in the left eye, but when examined in September 1962 (16 months post-irradiation) the retinal examination showed definite improvement. His visual acuities were now 20/25 with the right eye and 20/60 with the left.

DISCUSSION

There is little doubt that suppression of pituitary function by heavy particle radiation has been of benefit to many of these patients. The mechanism by which this is brought about is not understood. A suggested mechanism is the inhibition of growth hormone production, and C.H. Li and Moudgals have assayed the sera of three of our patients so-exposed to heavy particles (patients with breast cancer) and have found a fall in the values (26). It is to be noted that although insulin requirements fell in the low dose group (see Figure 2), we found little change in the output of the target-organ hormones at this lower dose level. With much higher doses, it is possible to completely destroy the pituitary gland by this method. This, however, may not be necessary, and we are continuing our investigations on the assumption that complete destruction is not necessary. In this connection it is interesting to know that Joplin, Fraser and others (27) have found no correlation between favorable response of retinopathy and degree of pituitary destruction, as measured by suppression of end-organ function.

The first three cases show the effects of complete or nearly complete hypophysectomy. In contrast to surgical hypophysectomy or complete hypophysectomy produced by implantation of radioactive materials into the pituitary, heavy particles produce a gradual loss of pituitary function. Previous reports (18) from this laboratory indicate that the onset of pituitary effect is related to both the total number of rads delivered and the rate of administration. The histologic changes in the hypophysis are also correlated with rate and size of dose (25). In this way it would appear to simulate the process of spontaneous hypopituitarism where there is often a gradual loss of trophic hormone activity. The first case demonstrated the marked degree of insulin sensitivity which occurs following hypophysectomy, and this remains a problem in her management. Except for one episode of retinal hemorrhage, her retinal-vascular changes have remained remarkably stable for more than five years, and she retains good visual acuity. There has been no apparent change in the areas of retinal fibrosis. The second case has a lesser degree of hypopituitarism and the diabetic management has been less difficult. The advanced changes in the right eye were uninfluenced by our therapy; the retinopathy in the left eye has remained quite stable. The third case showed a rather dramatic improvement in her retinopathy and visual acuity following pituitary irradiation. The left oculomotor nerve was partially damaged, probably secondary to radiation damage. The vascular complications of her diabetes were apparently uninfluenced, and she had several cerebral vascular accidents and died in renal failure.

Cases 4, 5 and 6 received lesser amounts of alpha-particle radiation. Cases 4 and 6 showed a fall in insulin requirements while Case 5 did not; the latter's period of follow-up was significantly less than the others. However, all of the patients showed some decrease in end-organ function, but none of them required cortisone or thyroid. Case 4 showed some improvement in his visual acuity related to resorption of vitreous hemorrhage. While he had no more hemorrhages, the areas of retinitis proliferans did not change in appearance. Other diabetic complications progressed and he died in advanced uremia. Case 5 again shows failure of pituitary irradiation to be of value in patients with advanced retinopathy and cardiovascular disease. This young patient died of a massive myocardial infarct 9 months after therapy. Case 6 had no renal or cardiovascular complications and his retinopathy has shown objective improvement. His funduscopic changes are depicted in Figure 3. His retinopathy was less advanced than that of many of the patients.

The size of the dosage in rads or roentgens and the duration of time over which it is administered, naturally, is of importance as it relates to functional and histologic effects on the pituitary gland. Whether the dosage is given through a technique which combines head rotation and the use of the Bragg curve, rotation alone or "straight through" radiation with the Bragg curve, is of course of importance. Over much of the Bragg curve the RBE is greater than one and probably of the order of 2 (9,10,11,14,28). The doses to most of our patients have been in the range 11,000 to 15,000 equivalent rad over the period of 11 days. However in a current

series of patients we are administering a smaller dose over only 5 days.

It is apparent from our studies that diabetics with advanced cardiovascular and renal complications are not desirable patients to treat with this method as has been noted by others attempting to reduce pituitary or adrenal function. In our experience so far the course of their vascular disease appears to be uninfluenced, and the retinopathy was seldom significantly improved. Therefore we are now attempting to avoid treating patients with far advanced nephropathy and vascular disease and hypertension.

All diabetic retinal changes are not improved by pituitary suppression. We have not observed retinitis proliferans to be significantly changed nor areas of fibrosis to regress. Patients with severe glaucoma or degenerative changes in the lens or other structures in the anterior portions of the eye have also not proved to be suitable candidates (see Case 5).

Current evidence (6,7) indicates that retinopathy can be influenced by hypophysectomy. Such questions as the degree of pituitary suppression required to produce these changes, the type of retinal lesions that respond, the duration of regressions when they occur and the physiological basis for such effects are as yet unanswered. Although our work demonstrates that retinopathy can be influenced by the so-called "atomic knife" delivering ablative or suppressive heavy particles to the pituitary fossa telatherapeutically, further study, long term follow-up and better understanding of the natural history of diabetic retinopathy will be necessary to solve several problems. Finally, the greater RBE of heavy particles,

and their favorable qualities (little scatter and great penetration) and the favorable depth dose-- skin dose relationship (Bragg curve) make them an excellent tool for the production of inhibitory or destructive lesions in the pituitary gland or elsewhere in the body. Because cyclotrons and accelerators capable of delivering these heavy particles are available in many centers (29,30), such studies as this can now be done in many parts of the world.

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FIGURE CAPTIONS

Figure 1. Changes in target-organ function following pituitary irradiation.

Figure 2. Changes in insulin requirements following pituitary irradiation.

Figure 3. Patient H.W. Superior temporal region, right eye. Before treatment (left) there was marked venous dilatation and irregularity; there were also numerous microaneurysms and many bleeding neovascular tufts. Sixteen months following irradiation (right) there is marked reduction in the neovascularization and the number of microaneurysms; there is also a striking improvement in the appearance of the retinal veins.

Figure 4. Patient R.F. Superior region, left eye. Before treatment (left) there were many microaneurysms, hemorrhagic neovascular tufts, and much exudate. Five months following therapy (right) there is marked reduction in microaneurysms and hemorrhagic spots, and much less exudate. Neovascularization is both better in some areas and worse in others; therefore, the net effect with regard to neovascularization is no change.

Table 1

PITUITARY IRRADIATION
DIABETIC RETINOPATHY

PATIENTS FOLLOWED 24-56 mon.	SEX	SURVIVAL Post- Irrad. (mon)	AT TIME OF IRRADIATION			RETINOPATHY Change, Post- Irradiation	GLAUCOMA Initial Status	CARDIOVASCULAR DISEASE Initial Status
			Age (yrs)	Duration Disease (yrs)	Duration Retinop. (yrs)			
1. CLF	F	56	37	14	<1	? Stabilized	Mild	None
2. KUG	M	51	48	21	1	? Stabilized	Moderate	Moderate
3. FEL	M	48	39	27	3	Stabilized	None	None
4. PRO	M	48	36	22	1	Stabilized	None	None
5. KRN	M	35	50	1	1	Stabilized*	Moderate	Advanced
6. ELL	F	33**	24	13	3	Stabilized*	Mild	None
7. DUN	M	33**	33	16	2	Stabilized*	Advanced	Advanced
8. HLT	M	32	59	1	1	Progressed	None	None
9. MAZ	F	31**	44	10	6	Progressed	Mild	Moderate
10. YTZ	M	31	41	13	1	Progressed	None	None
11. EMR	F	30	35	12	12	Progressed	Mild	Mild
12. KLY	F	30	61	1	1	Stabilized*	None	None
13. R.SM	M	28**	55	1	<1	Progressed	Moderate	None
14. RUB	M	28	48	26	1	Progressed	Mild	None
15. BUL	M	28	36	21	<1	Progressed	Advanced	Advanced
16. McL	F	28	52	26	6	Stabilized	None	None
17. EVT	M	26**	58	15	2	Stabilized*	Mild	Mild
18. CAR	F	26	53	16	1	Stabilized	None	None
19. SCM	M	25	40	22	2	Stabilized*	Moderate	None
20. KOM	M	24	33	21	8	Stabilized	Mild	Mild

* Vision Improved

Compiled 11-30-62

**Deceased patient

Table 2

PITUITARY IRRADIATION
DIABETIC RETINOPATHY

PATIENTS FOLLOWED 12-23 mon.	SEX	SURVIVAL Post- Irrad. (mon)	AT TIME OF IRRADIATION			RETINOPATHY Change, Post- Irradiation	NEPHROPATHY Initial Status	CARDIOVASCULAR DISEASE Initial Status
			Age (yrs)	Duration Disease (yrs)	Duration Retinop. (yrs)			
1. DVD	M	23	40	10	<1	Stabilized	Mild	None
2. CLV	M	23	29	26	14	Stabilized	Moderate	Moderate
3. HOW	F	21	34	13	<1	Progressed	Moderate	Moderate
4. MRG	M	20	27	17	2	Stabilized	Moderate	Moderate
5. ELZ	M	20	34	22	1	Progressed	None	None
6. McC	F	18	36	23	12	Progressed	None	None
7. TOR	M	18	48	9	1	? Progressed	Mild	Mild
8. KLTZ	F	18	35	29	2	Progressed	Mild	None
9. WIL	M	18	21	18	8	Stabilized*	None	None
10. JEN	M	17	36	27	2	Stabilized	Moderate	Mild
11. DAN	M	16**	37	19	4	Progressed	Advanced	None
12. DVS	M	16	65	16	1	Stabilized*	None	Mild
13. HAF	M	14**	36	11	1	? Stabilized	Mild	None
14. RYL	F	13	48	15	1	Stabilized	Mild	None
15. A.SM	M	13	25	15	<1	Progressed	Advanced	Advanced
16. TIF	M	13	47	25	5	Stabilized	None	None
17. KTB	M	13	47	17	1	Progressed	Mild	Mild
18. KNP	F	13	28	22	10	Progressed	Mild	Mild
19. BWR	M	12	30	28	1	Progressed	None	None
20. BLK	F	12	55	16	3	Stabilized*	None	None
21. PAT	M	12	36	31	5	Stabilized	Mild	Mild

*Vision Improved

Compiled 11-30-62

** Deceased patient

Table 3

PITUITARY IRRADIATION
DIABETIC RETINOPATHY

PATIENTS FOLLOWED 4-11 mon.	SEX	SURVIVAL Post- Irrad. (mon)	AT TIME OF IRRADIATION			RETINOPATHY Change, Post- Irradiation	NEPHROPATHY Initial Status	CARDIOVASCULAR DISEASE Initial Status
			Age (yrs)	Duration Disease (yrs)	Duration Retinop. (yrs)			
1. ANS	M	11	64	25	2	Stabilized	None	Mild
2. ROM	M	9**	22	17	<1	Progressed	Advanced	Advanced
3. REG	M	9	54	21	2	Progressed	None	Mild
4. WKR	F	9	37	24	6	Stabilized	None	None
5. HYS	F	9	29	16	3	Stabilized*	Moderate	Moderate
6. WAT	F	9	35	10	<1	Stabilized*	Moderate	Moderate
7. BNS	M	8	23	22	1	Stabilized*	Moderate	None
8. McN	M	8	31	15	2	Stabilized*	None	None
9. FRD	F	8	32	22	1	Progressed	Advanced	Mild
10. BRZ	F	8	37	8	2	Stabilized	Mild	Mild
11. SKL	F	7**	35	10	1	Progressed	Advanced	Advanced
12. WUN	F	7**	24	16	<1	Progressed	Advanced	Advanced
13. GOL	F	6	26	12	2	Stabilized	None	None
14. WAD	M	6	33	13	1	Stabilized	None	None
15. DSY	F	6	54	19	3	Stabilized	None	None
16. MUL	M	6	42	18	2	Stabilized	Moderate	None
17. KEN	M	6	27	16	9	Stabilized*	None	None
18. WTH	M	6	41	6	1	Progressed	None	Moderate
19. SIG	M	6	58	8	3	Stabilized	Mild	Mild
20. SCHN	M	4**	37	4	4	Stabilized	Advanced	Advanced

*Vision improved.

Compiled 11-30-62

** Deceased patient

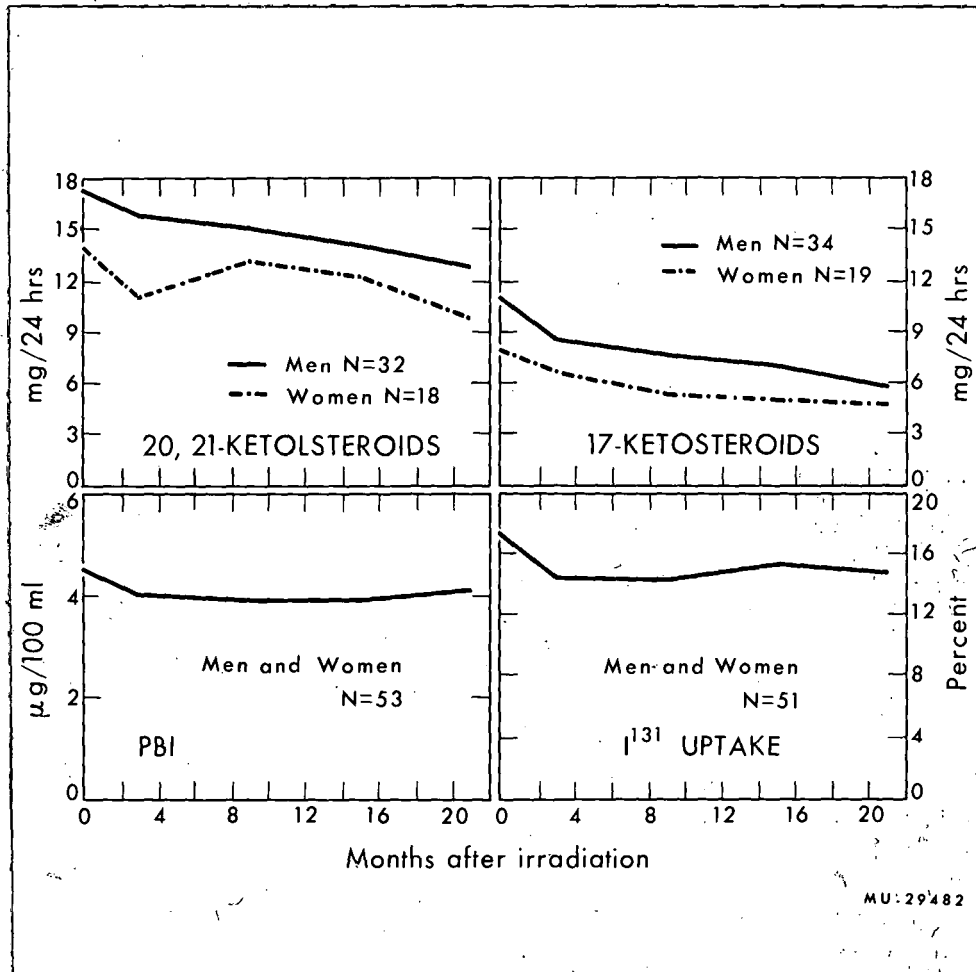


Fig. 1.

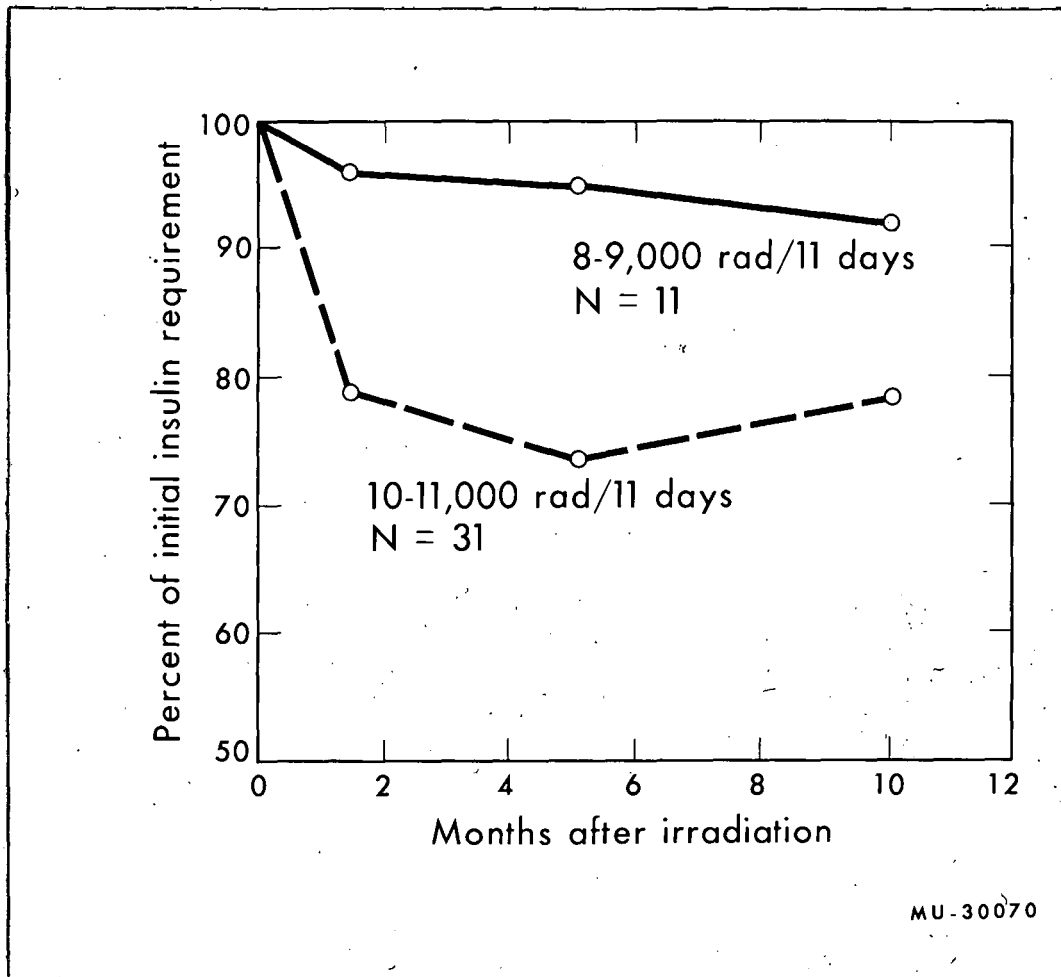


Fig. 2.

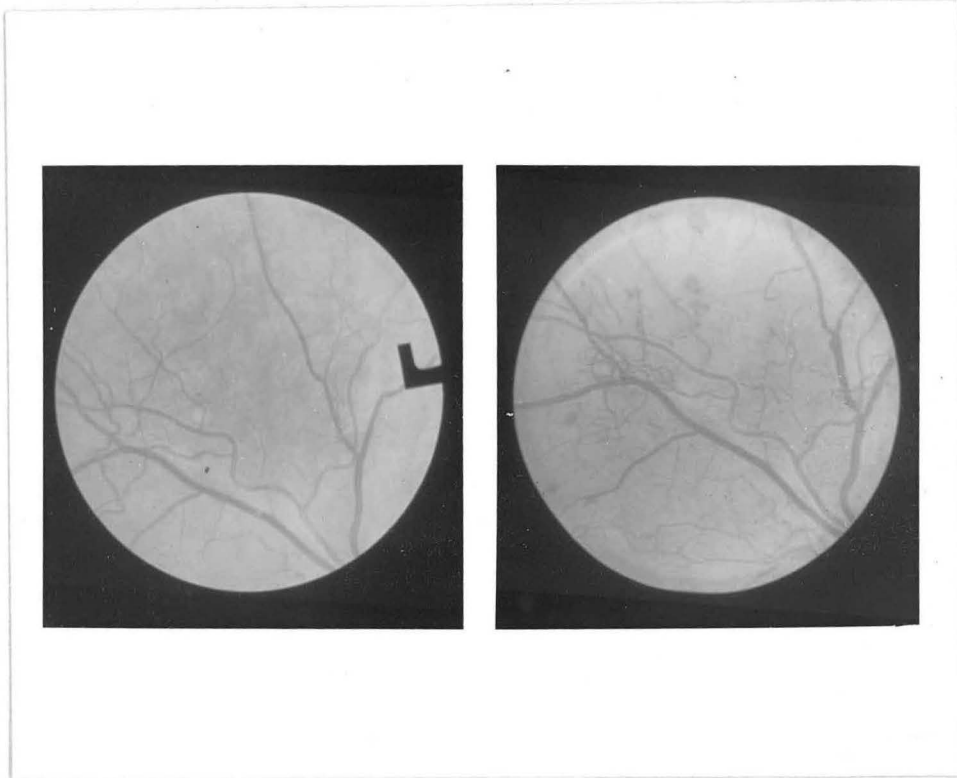


Fig. 3.

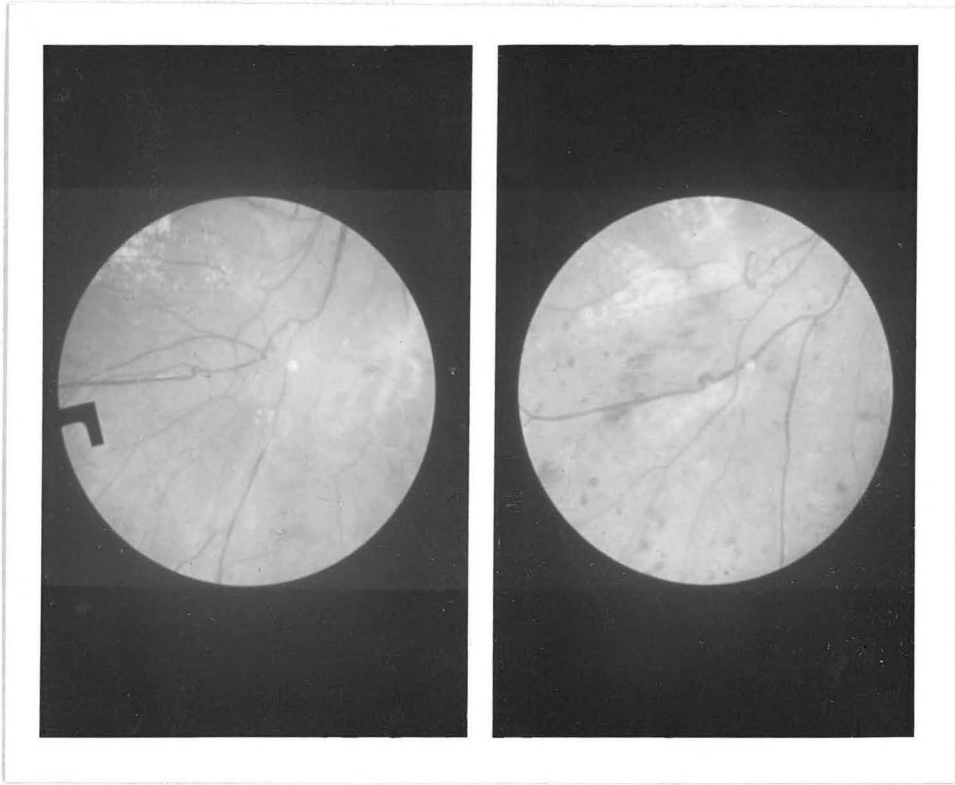


Fig. 4.

Case 12 #6

Page
501

