Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Pituitary Tumors
Carcinoma of Breast

Volume XVIII | Friday, March 14, 1947 | Number 19

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume XVIII | Friday, March 14, 1947 | Number 19

INDEX

Published for the General Staff Meeting each week during the school year, October to June, inclusive.

Financed by the Citizens Aid Society, Alumni and Friends.

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

March 17 - March 22, 1947

No. 149

Monday, March 17

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - Roentgenology-Medicine Conference; Veterans' Hospital.

11:00 - 12:00 Physical Medicine Conference; Skin Temperature Measurements; George K. Stillwell; W-200 U. H.

12:15 - 1:15 Obstetrics and Gynecology Journal Club; M 435, U. H.

12:30 - 1:20 Pathology Seminar; Malignant Tumors of the Small Intestine; Jack Friedman; 104 I. A.

Tuesday, March 18

9:00 - 9:50 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - Surgery Reading Conference; John R. Paine; Small Conference Room, Bldg. I, Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology; H. E. Michelson and Staff; Veterans' Hospital, Bldg. III.

3:15 - 4:15 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - Clinical Pathological Conference; Veterans' Hospital.

3:45 - 5:00 Pediatrics Staff Rounds; I. McQuarrie and Staff; W-205, U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; M-515, U. H.

8:00 - Minnesota Pathological Society; Bulbar Poliomyelitis. New Interpretations of the Clinical-Pathological Picture; A. B. Baker: Physiological Problems in Poliomyelitis; M. B. Visscher; Medical Science Amphitheater.

Wednesday, March 19

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 10:00 Psychiatry and Neurology Seminar; Station 60 Lounge; U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Chronic Lymphatic Leukemia; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:00 - 1:00 Physiological Chemistry Journal Club; Staff; 116 M. H.

4:00 - 6:00 Medicine and Pediatrics Infectious Disease Rounds; W-205, U. H.

Thursday, March 20

8:30 - Surgery Grand Rounds; John R. Paine and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff. Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - Roentgenology-Surgery Conference; Veterans' Hospital.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Congenital Dislocation of the Hip; Donald Lannin; M-515 U. H.

7:30 - Physical Medicine Seminar; 111 Mes.

Friday, March 21

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:00 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - Medicine Grand Rounds; Veterans' Hospital.

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

11:30 - 1:00 University of Minnesota Hospitals General Staff Meeting; Unilateral Exophthalmos; John H. Peterson; New Powell Hall Amphitheater.

1:00 - 2:00 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff; Todd Amphitheater, U. H.

Saturday, March 8

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

9:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

II. RADIATION THERAPY OF PITUITARY TUMORS

Harry W. Mixer

Early History

Credit for the first treatment of a pituitary tumor with x-rays is generally given to Gramegna.[1] He reported in 1909 to have treated an acromegalic in 1907. Following this treatment, the patient showed some improvement which was, however, only temporary. This case must have been treated with very low voltage and little or no filtration. Hence, it is quite remarkable that there was any improvement in view of the small dose which the tumor itself must have received. Later in 1909 Beclere[2] also reported a case in which headaches and visual disturbances were improved by irradiation of the pituitary. In 1914 the latter author[3] reported 4 additional cases, 3 of which were acromegalics, with some improvement in each case. In 1922 the same author[4] reported that his original case, an acromegalic, was still in excellent health 13 years after treatment. Kupferle and von Szily[5] in 1915 were the first to report a case treated with radiation following surgery. The surgical procedure produced only slight improvement for about 6 months. Then when vision began to fail, roentgen therapy was given with marked improvement in vision 8 weeks after the therapy.

Since these early beginnings, many series of cases treated by radiation, surgery, or both have been published. These various reports will be referred to in the discussion which follows.

Pathology and Clinical Signs and Symptoms

At the present time, adenomas of the pituitary are divided into 3 main types - chromophobe, acidophile, and basophile. These are named according to the type of cell (normally occurring in the anterior lobe of the pituitary) which has proliferated to the greatest extent.

The percentages of the various types of tumors are given by different authors. Costello[6] reported in 1935 that in a series of 1,000 routine autopsy pituitaries, there were 140 chromophobic, 20 acidophilic, and 72 basophilic adenomas. All of these were very small tumors. In Cushing's[7] 338 pituitary tumors from 1913-1932, there were 260 chromophobic, 67 acidophilic, 11 adenocarcinoma, and no basophilic adenoma. Kerr and Cooper[8] in 1942 reported a series of 31 chromophobic, 9 acidophilic, and 1 basophilic on clinical diagnosis.

The chromophobe adenoma, which is the most common type, gives rise to pressure symptoms and some hypopituitary changes. These adenomas may invade the sphenoid or erode into the cranial cavity. In such cases, they are referred to as "malignant adenoma" or carcinoma even though there are no distant metastases. Cystic degeneration of chromophobe anenomas occurs quite commonly. Groff[9] in 1942 reported a 25% incidence of cystic degeneration of chromophobe adenomas. In Cushing's 338 pituitary cases reported in 1939 by Henderson[7], 17% proved to be cystic as shown by surgery. Schnitker[10] in 1939 reported 11 cystic chromophobe adenomas in his series of 81 surgical cases. In a series of 23 cases reported by Rand and Taylor[11] in 1935, 3 were reported as cystic. The importance of cyst formation in relation to therapy will be discussed later.

Acidophilic adenomas are composed of eosinophilic cells and are almost always associated with body growth changes. These tumors are usually less invasive than chromophobic tumors and much less frequently become cystic. They frequently produce local pressure effects.

Basophilic adenomas, which usually do not cause significant enlargement of the pituitary gland, practically never produce local pressure effects. They are composed of the basophilic cells of the pituitary. If of sufficient size they produce the syndrome first described by Cushing[12] in 1932 as pituitary basophilism. Since that time, however, it has been found that other conditions can produce the same syndrome. In 1935 Cooke[13] described a change in the basophile cells of the pituitary gland which were common to conditions exhibiting the syndrome attributed to basophilic adenoma. This he described as a hyaline

change in the basophile cells of the pituitary which did not appear to represent effects of degeneration but altered physiological activity. This condition was found in a slight amount in only 9 out of 350 pituitary glands not associated with basophilism. It was found, however, in a large amount in many basophile cells in all 12 available examples of basophilism whether associated with a basophilic adenoma, a neoplasm of the thymus, or a neoplasm of the suprarenal cortex. This was the only abnormality common to all 12 examples of the syndrome and it was concluded by Crooke that it was the abnormality of fundamental significance. Hence, it is important to note that basophilism is not always associated with a pituitary adenoma, but that it is usually accompanied by a pituitary change. Eisenhardt and Thompson[14] in 1939 reported a series of 67 cases of basophilism, 58 of which were shown to have definite pituitary adenoma at necropsy. They further reported that "Crooke" cells do not appear in the cells comprising the adenoma of the pituitary even if one is present. Furthermore, they believed that "the hyalinization" represents a degenerative change following a period of physiological overactivity of the basophils as a recpirocal consequence of inactivation of certain subsidiary ductless glands.

The signs and symptoms of pituitary tumors in general can be divided into 2 groups - Endocrine symptoms and neighborhood symptoms. In general, the most frequent pituitary tumor symptoms are headache and failing vision. Headache is present at some time or other in about 3/4 of the cases. It may disappear quite suddenly, probably when the tumor decompresses into the sphenoid or breaks through the diaphragm sella. Visual disturbances appear first in about 2/3 of the cases. This consists of blurring of vision and constriction of the visual fields. Diplopia may also be present. Endocrine complaints are also very common. Objective findings are optic atrophy, hemianopsia, decrease in visual acuity, deformity of sella and endocrine changes.

Chromophobe adenomas are characterized by both glandular and neighborhood symptoms. The glandular symptoms are not due to over secretion by the tumor but are due to undersecretion of the remainder of the pituitary caused by the compression of the tumor tissue. Hence, these are hypopituitary symptoms and may be represented by obesity, low BMR, mental sluggishness, scant fine silky, and dry hair, dry pale and soft skin, and low carbohydrate tolerance. The male may exhibit a loss of libido and potency, sterility, and scantiness of facial hair. The female may be amenorrheic and sterile. The chief neighborhood symptom is headache which is probably due to the increased pressure on the diaphragm sella. Enlargement of the pituitary fossa is also due to the pressure ane erosive effects of the tumor. Objective eye changes usually in the form of bi-temporal hemianopsia, decrease in visual acuity, and optic atrophy is likewise due to the effects of pressure and traction on the optic nerves and chiasm plus blockage of the nerve blood supply. Schnitker[10] in 1938 reported on a series of 88 cases of chromophobe adenoma patients, 77 of which entered the hospital because of failing vision. 86 of the entire group were found on careful examination to have visual defects, however. 82 showed optic atrophy and 4 had early choke. Visual field defects usually begin as bi-temporal upper quadrantopsias then progress to bi-temporal hemianopsias, generalized constriction of the visual field, and finally blindness. Other field defects may be present depending on the location of the tumor and chiasm.

The acidophilic tumors may also show both glandular and neighborhood symptoms. The glandular symptoms are either gigantism or acromegaly depending on the age of the patient. The acromegalic patient usually presents a very typical clinical picture. The main signs are enlargement and prominence of the lower jaw, prominent supraorbital ridges, a spade-like enlargement of the hands and feet, a thickening and puffiness of the skin, enlargement of the frontal sinuses, nose, and lips, and a thickening of the tongue. General bodily weakness and mental dullness may also be present. There may also be sexual changes such as loss of libido and menstrual irregularities. The female tends to change toward the masculine body type with increased growth

of body hair and decrease in the pitch of the voice. Neighborhood symptoms are the same as those of the chromophobe tumor. Headache, decrease in visual acuity, bitemporal hemianopsia, sella turcica changes and optic atrophy may be present but are usually not as prominent as in the case of the chromophobe tumors. It is quite common for acidophile tumors to apparently "burn out" and cause a spontaneous remission of some symptoms such as headache and a cessation of the progression of other symptoms such as the acromegalic features. This must be considered in the evaluation of any type of treatment.

Basophilic adenoma rarely produce neighborhood symptoms but many glandular symptoms which are very characteristic. The syndrome was originally described in 1932 by Cushing[12] and is known as Cushing's syndrome or Pituitary Basophilism. The most important clinical features are trunk and neck obesity which spares the extremities, bison type neck, round "moon-like" face, purple striae on abdomen, purpuric tendency, hypertension, osteoporosis (especially of the spine), signs and symptoms of diabetes mellitus, amenorrhea in females, sexual impotence in males, hypertrichosis of face and trunk in females, loss of scalp hair, extreme susceptibility to infections and general bodily weakness. Headaches and visual disturbances are usually absent.

Evaluation of Results

There are in general 3 agents used in the therapy of pituitary tumors. These are surgery, radiation and endocrines. Before the efficacy of a certain method of therapy can be judged, criterion of improvement or effect of therapy must be set up. The results of therapy in malignant diseases are commonly expressed in the form of survival rates for a certain number of years. Since pituitary tumors in general are not fatal lesions, this method cannot be used. One of the best criterion of the effect of therapy in chromophobe adenomas is the restoration of or the improvement of useful vision. It is important that one follows both the peripheral visual fields and the visual acuity. Without complete knowledge of both, it is difficult to form an accurate opinion of the effect of therapy. Usually with an improvement in the visual fields, there is a concomitant improvement in visual acuity. However, in some cases there may be a marked constriction of the visual fields with uninvolved macular areas and consequent normal visual acuity. Improvement in the visual fields will not be reflected in improvement of the visual acuity in such a case. Conversely the decrease in the visual field may involve the macular region in which case the visual acuity will be greatly decreased. Then a very slight imperceptible improvement in the visual field may be accompanied by marked improvement in visual acuity and useful vision be restored. Optic atrophy should also be carefully followed. Disappearance of headaches is also an important criterion. One should also depend on the degree of restoration of normal health, the return of general well being, and the disappearance of hypopituitary symptoms. The duration of improvement should also be considered.

Results in the acromegalic group must be judged in a similar fashion. Improvement in visual acuity and fields as described above should be considered. Disappearance of headaches and regression of or cessation in the progress of the acromegalic features are important criterion. Reappearance of normal menstruation is an important sign of improvement.

When considering the effect of treatment of Cushing's syndrome, one must consider the improvement of the patient's general health and the change of the endocrine symptoms previously mentioned. Disappearance of lethargy and weakness, improvement of diabetes, change of facies and body contour, fading of purpura and purple striae, decrease in the incidence of infections and the absence of hirsutism must also be considered. In addition survival rates can be used in that without therapy most of the cases end with quite rapid fatality. The chief difficulty in judging the effects of radiation therapy in the treatment of Cushing's syndrome is the difficulty in determining which of the several possible pathological conditions is responsible for the case being considered. Hence, one must make every effort to rule

out other possible lesions by exhausitve use of the diagnostic methods now available. When evaluating results, one must remember that patients with pituitary adenomas may have spontaneous remissions without therapy. Chromophobe tumors may break into the sphenoid sinus to give remarkable relief and acidophilic tumors may become "burned out" with a cessation of the progression of the disease spontaneously. The same may occur in Cushing's Syndrome.

Therapy

It is generally agreed by those acquainted with pituitary tumor therapy that radiation therapy is the treatment of choice in cases of acromegaly and basophilism. However, there is a considerable amount of controversy at present concerning the advisability of surgery, radiation, or both and in what order in chromophobe adenoma cases. Radiologists in general believe that radiation therapy is the preferred treatment in certain cases while surgeons are of the opinion that surgical therapy should be instituted in the same cases.

The object of treatment of pituitary tumors is two-fold. The first effort is to prevent the destruction of or to improve the remaining vision. This is the most important consideration. The second is the attempt to increase pituitary secretions in the case of the chromophobe adenomas and to decrease abnormal secretions in the case of the acidophile or basophile adenomas. During the past 35 years many authors have presented series and case reports which have tended to emphasize various combinations of therapy for pituitary adenoma.

O. Hirsch[15] in 1921 was the first to report a series of pituitary adenomas treated with radiation. This series of 28 cases was treated postoperatively with radium. He concluded from this series that only cystic pituitary adenomas could be cured by surgery alone and that acidophile and solid chromophobe tumors required radium. Of the latter 2, Hirsch was of the opinion that the acromegalics responded best to radiation therapy. In 1925 Dott and Bailey[16] reported on the clinical and pathological features of 162 of Cushing's cases and incidentally mentioned that they advocated a trial of radiation therapy unless there was imminent danger of loss of vision. Surgery should then be used, if radiation did not stop the progress of the visual defect. They also recommended post-operative x-ray therapy. Guarini[17] in 1925 reported 4 cases of pituitary tumor, one of which was an acidophile adenoma. These were treated with xOray with improvement in all cases. Visual fields and acuity improved together with beneficial effects on diminished libido and on amenorrhea. It is interesting to note that he also reported a decrease in the size of the soft parts of the terminal portions of the extremities in acromegaly. He recommended x-rays as the treatment of choice in hypophyseal tumors. Heinismann and Czerny[18] in 1926 reported 6 cases of acromegaly all of which had definite improvement with x-ray therapy to the pituitary. Schenderow and Kopelmann [19] in 1926 reported 11 cases of acromegaly with marked improvement of headache and vision in 10 cases. The acromegalic symptoms, however, were not affected. They recommended Roentgen Therapy in acromegaly and surgery in cases refractory to radiation. Beclere[20] in 1929 wrote another of his series of papers in which he states that roentgen therapy should only be used with the understanding that it is to be followed by surgical removal of the pituitary tumor if the radiation fails to produce results. He also recommended several portals rather than one through the nasopharynx.

Towne,[21] a neurosurgeon, in 1930 reported a collection of 5 cases, in which there was one case with normal vision and fields for 5 years after radiation with recurrence of symptoms and failure of repeated radiation and final evacuation of a cyst followed by improvement; 1 with bi-temporal hemianopsia not improved by radiation and refusing surgery; 1 blind 3 months with slight response to radiation and no response to surgery; and 1 with bi-temporal hemianopsia relieved by radiation for 3 years. From his own and others' statistics, Towne concluded that cystic tumors could be cured by surgery only. He also showed that about 80% of patients with operation only showed a recurrence of symptoms within 2 years.

He implied that improvement due to radiation was much longer lasting. He advised that radiation be given a 6 months' trial, as long as there was no further visual loss, before surgery be resorted to.

Dyke and Gross[22] reported 5 cases in 1931. Four were chromophobe adenomas, and one was an acidophil. All had marked relief of headache, 3 had marked improvement in fields and acuity, and 2 showed no further loss of vision. Two lost considerable weight. The radiation technique was 2 temporal and 1 anterior fields; 155 Kv with 0.5 mm. of copper and 1 mm. of aluminum filter, 2000 r to all ports repeated after 5 weeks. Five series were given. Hence, the total dose to the pituitary was quite high.

Harris and Selinsky[23] in 1932 presented 13 cases of pituitary tumor treated at 180-200 Kv with 1 mm. of aluminum and 0.5 mm. of copper filter, 1 frontal and 2 temporal fields with about 860 r to each field. Three of 5 cases with headache had relief, 8 of 11 cases with visual disturbances were benefited, 3 of 5 cases with polydypsia were improved and 3 of 4 cases of acromegaly showed regression of skeletal overgrowth. The authors concluded that cystic tumors responded poorly to radiation. They recommended a therapeutic trial with radiotherapy before resorting to surgery.

Cushing[12] in 1932 stated that radiotherapeusis of pituitary adenomas would eventually come to be discarded. This opinion was apparently based on only 10 cases of pituitary adenoma treated with preoperative radiation. No case was followed for more than one month and there was marked improvement in only one case. Globus[24] speaking in the same vein in 1933 stated that radiation therapy of the pituitary did little more than give rise to false hopes only to be followed by an explosive reappearance after a temporary arrest.

Rand and Taylor[11] in 1935 on the basis of 23 pituitary tumor cases concluded that acidophile tumors react most favorably to radiation. They further stated that chromophobe tumors do not respond uniformly and that cystic tumors show no improvement with radiation. They could detect no definite regression of acromegalic symptoms following irradiation. These authors treated with 186 Kv. x-rays.

Dyke[25] in 1935 reported a series of 20 chromophobe tumor cases in which 25% had improved vision and 75% were relieved of headache, lethargy and diplopia after radiation therapy. He found that headache may disappear as early as 48 hours after a single dose. He also concluded that x-ray had no effect on cystic cases.

Pfahler and Spuckman[26] in 1935 reported 21 cases and concluded that solid tumors respond well while cystic tumors responded poorly to radiation. They recommended a 2 month's trial of radiation to be followed then by surgery if no benefits were evident.

Dyke and Hare[27] in 1936 reported a series of 63 cases of pituitary adenoma. Of these 38 were chromophobe and 25 acidophil. Of the 38 chromophone patients, 10 showed improvement in vision and 10 showed arrest of the progressive loss of vision. The remainder became worse. These authors recommended that on the basis of this experience, a trial of radiation therapy be given in cases of chromophobe adenoma unless the patients vision is close to blindness. If there is no further loss of vision, surgery should not be performed. If vision continues to become worse after a trial of radiation therapy, then surgery plus postoperative radiation therapy is indicated according to these authors. Of the 25 acidophilic tumor patients treated, 10 showed improvement in vision and 9 showed arrest of the progressive loss of vision. The other 6 became worse. Hence these authors recommend a trial of radiation therapy with careful follow-up and surgical intervention if the results are not satisfactory with radiation alone.

Hansen[28] in 1936 presented the case history of a patient with Cushing's syndrome treated with x-ray therapy of the pituitary. He states that x-ray treatment decreased hyperglycemia; urinary output of calcium, nitrogen, and ammonia; and hypertension. It did not affect the fat distribution in his

case. The patient was definitely improved.

In 1937 Sosman[29] presented a review of the subject of irradiation therapy of pituitary tumors. He concluded that in cases with chromophobe adenomas good results could be expected in well over 50 per cent of the cases with radiation alone. He recommended that radiation therapy be given a trial in all cases of chromophone adenoma with 6 months observation before resorting to surgical removal of the tumor. If this therapy failed, then he believed surgery was indicated.

He also reported the results of radiation therapy of 3 cases of pituitary basophilism. One patient died shortly after radiation therapy with no definite evidence of improvement. The other 2 showed striking subjective and objective improvement. One of the latter cases was the original case of Cushing[12] previously reported in 1932.

Schnitker, Cutler, Bailey, and Vaughan reported in 1938 on 81 chromophobe adenomas verified by operation. Forty-two of these were treated with radiation and opeation while 33 were treated by operation only. Eleven tumors were cystic. Six of these were irradiated with no response in 4 and slight improvement in 2. Of 33 cases with operation only, the average duration of visual improvement was 3 years, while of 42 cases with operation and radiation the average duration of improvement was 4 years. Therapy was given at 185 Kv. with several series at 6 week intervals. The patient's complaint of lassitude for 2 to 4 weeks after irradiation was mentioned. The authors contended that as much immediate improvement was obtained with biopsy of the pituitary as with radical exterpation of the gland. They concluded that unless there is an urgent need for saving vision that one should try a course of radiation therapy before using surgery.

Vaughan[30] in 1938 reported 26 cases of acromegaly treated with radiation. The author stated that headache might disappear as quickly as 3 hours after the initial therapy. Bony changes were permanent but the soft tissue features might improve to cause decrease in the size of hands and feet. He concluded that radiation therapy was the method of choice and should be used before surgery unless a danger of permanent loss of vision was present.

Sosman[31] in 1939 reported 28 acromegalics in which headache was relieved by radiation therapy in 90% of the cases. Eight cases of chromophobe tumor with sufficient follow-up to allow evaluation were reported. Seven of these received marked benefits from irradiation alone with restoration of vision and normal living.

Grant[32] in 1939 described 84 cases all receiving surgical therapy and some receiving radiation in addition. He concluded on the basis of visual efficiency that operation followed by irradiation produced the best results. But that radiation therapy should be tried first with 3 weeks observation.

Henderson[7] in 1939 wrote an excellent review of Pituitary Adenomas and analyzed Cushing's 338 cases. His conclusions were that operation plus irradiation produced the best results. The total operative mortality in these cases was 4.9%. During the last 10 year period, this figure was 2.4%. He concluded that vision might return in an eye blind for as long as 3 months. Radon implantation was abandoned because of the danger of bone necrosis and meningitis. He stated that surgery may have no effect on the headache of an acromegalic patient, but that radiation when later applied might completely relieve the patient of this symptom.

Eisenhardt and Thompson[14] in 1939 reported on a collection of 67 cases of basophilism. Fifty-eight of these showed pituitary adenoma at post mortem. Eighteen of the 67 cases were treated with radiation. Eleven of these received some benefit from the therapy.

Kerr and Cooper[8] in 1942 reported 25 cases of pituitary tumors treated with radiation alone. One of 2 acromegalics made an excellent reponse with decrease in the size of the hands and feet; 18 of 21 chromophobe tumors made good response; while 2 chromophobe cystic tumors showed poor response. This author

used 200 Kv with thoreaus filter and 5 ports. Each port was given a total of 1800 r in air.

Dyke and Davidoff[33] in 1942 reported 3 cases of Cushing's syndrome with no response in any of the cases to radiation therapy of the pituitary. However, in view of other favorable reports these authors recommend a trial of radiation therapy to the pituitary with the hope that the case in question might respond favorably to the treatment. In cases without response to radiation therapy, they suggest that radiation of the adrenals might prove beneficial if adrenal tumors are either primarily or secondarily responsible for the disease in such a patient.

Crooke[34] in 1944 reported one case of Cushing's syndrome with remarkable improvement following x-ray therapy to the pituitary followed by implantation of the gland with radon seeds. He quotes Pattison and Swan (1938) who report two similar cases with remarkable improvement.

Luft[36] in 1946 reported his results in radiation of the pituitary in 8 cases of Cushing's syndrome. In 3 cases all symptoms disappeared, in a fourth only osteoparosis remained, and in a 5th only a decreased glucose tolerance was present after therapy. The 6th case showed considerable improvement but committed suicide; the 7th died of circulatory insufficiency but showed some improvement following therapy; the eighth patient was improved somewhat and able to go back to work but still showed the Cushing habitus. Luft suggests the following schedule of treatment in Cushing's syndrome: Exclusion of an adrenal cortical tumor or ovarian tumor by means of determination of urinary ketosteroids and pelvic examination; then a trial of radiation therapy to the pituitary, androgenic hormone, and pituitary surgery as a last resort.

Peyton[37] emphasizes the point that the neurosurgeon should see all cases of pituitary tumors before therapy is begun. Even if x-ray is probably the treatment of choice in a certain patient, the neurosurgeon should have the opportunity to review the case before therapy and to offer his recommendations as to the course of therapy to be followed. He further emphasizes that arrangements should always be made for frequent repeated checks of visual acuity and fields following any type of therapy and especially radiation therapy. If visual defects are slight and are not progressing rapidly, he believes that radiation therapy may be given a trial in chromophobe adenoma patients. Such patients must have careful follow-up of visual fields and acuity at frequent intervals so that surgery may be instituted if visual loss progresses.

Table 1

Cushing's Syndrome

Author	No. Cases	Results from X-ray therapy	Recommendations - Conclusions
Cushing 1932	1	Remarkable improvement	First to recommend x-ray Rx.
Hansen 1936	1	Definite improvement	
Sosman 1937	2	1 remarkable improve. 1 died, no improv.	If sufficient radiation applied should expect good results
Eisenhardt 1938	18	11 improve.	
Pattison 1938	2	2 remarkable improv. with radon implants	
Dyke 1942	3	3 no response	X-ray to pituitary should be tried. Possibly to adrenals also.
Crooke 1944	1	Remarkable improvement with radon implants & xray	X-ray to pituitary should cure if large enough dose given.

Table 1 (Cont.)

Cushing's Syndrome

Author	No. Cases	Results from X-ray Therapy	Recommendations - Conclusions
Luft 1946	8	5 remarkable permanent improvement	X-ray to pituitary is Therapy of choice.
TOTAL	36	22 (61%) definite improvement	

Summary of Therapeutic Results and Recommendations Collected from Publications by Other Authors

Cushing's Syndrome

Results of radiation therapy to the pituitary in Cushing's syndrome as reported in previous publications are summarized in Table 1. Twenty two, or 61% of 36 cases reported in this series of papers experienced definite improvement. In several of the cases the various authors observed remarkable prolonged improvement in endocrine symptoms and even complete cures. The failures could possibly be explained on the basis of insufficient radiation to the pituitary or on the basis of primary adrenal involvement or ovarian tumors. In view of the remarkable improvement reported in several cases, most authors recommend radiation therapy to the pituitary as the treatment of choice in Cushing's syndrome. Furthermore, it is well known that these patients are poor surgical risks and that untreated patients have an unfavorable prognosis. Hence a relatively conservative type of therapy such as x-ray to the pituitary, which has been shown to produce definite therapeutic results in an otherwise disabling and fatal disease, should certainly be given a trial before more radical therapy is undertaken. Injection with various hormones has been reported as being successful in a few cases and might also be tried. Radiation of the adrenal glands has been of some benefit in a few cases, and is another type of non-surgical therapy which could be used in cases refractory to pituitary irradiation. If this fails surgical exploration for an adrenal tumor might be indicated in cases in which an adrenal change is suspected or has been demonstrated by adrenograms or changes in excretion of ketosteroids. Adrenal changes apparently may be the primary pathology in some cases. In other cases adrenal changes are believed to be secondary to the pituitary adenoma. Surgical exploration of the pituitary would probably be the last alternative and would be indicated if severe visual defects are present which had not responded to radiation. Also if visual field changes and skull films suggest that the syndrome is definitely on the basis of an actual pituitary tumor and there has been no relief of endocrine symptoms by radiation of the pituitary, pituitary surgery should probably be tried.

Acromegaly

Table 2 summarizes the results obtained by various authors following radiation to the pituitary of acromegalic patients. Ninety-three, or 72%, of a total of 128 cases treated by the investigators included in this table obtained definite improvement in vision and endocrine symptoms. In most of these the improvement was maintained indefinitely. Most authors agree that patients with eosinophilic adenomas of the pituitary more frequently respond favorably to radiation therapy than do patients with chromophobe adenomas. In addition, the surgical approach to the pituitary in acromegalics is more difficult because of skull changes. Also these patients are frequently not good surgical risks because of secondary endocrine changes. Consequently it is quite generally agreed that radiation therapy is the treatment of choice in acromegalic patients. If very close follow-up of the patient and his v sion reveals that the condition is progressing following adequate radiation therapy, surgical intervention is indicated. Some investigators suggest that radiation therapy relieves symptoms due to endocrine secretion by the tumor which are not relieved by surgical therapy alone. Consequently if surgery is used first to relieve severe visual defects, it should be followed by a course of

Table 2

Acromegaly

Author-Date	No. Cases	Results from X-ray Therapy	Recommendations - Conclusions
Gramegna-09	1	Some temporary improvement.	
Beclere-09	1	Definite improvement.	
Beclere-14	3	Definite improvement in all.	Use multiple ports.
Roussy-24	1	Definite improvement.	X-ray yields cure or arrest of disease.
Guarini-25	1	Definite improvement.	X-ray is therapy of choice.
Heinismann-26	6	6 definite improvement.	
Schenderow-28	11	10 marked improvement.	X-ray preferred, surgery if refractory.
Marburg-30	7	6 definite improvement.	
Dyke -31	1	Definite improvement.	
Harris-32	4	2 definite improvement.	X-ray preferred, surgery if refractory.
Rand-35	5	5 definite improvement.	X-ray is therapy of choice.
Pfahler-35	6	3 definite improvement.	
Vaughan-38	26	17 definite improvement.	X-ray preferred unless visual loss is severe. If no improvement repeat in 2 months.
Sosman-39	28	25 definite improvement.	X-ray is therapy of choice.
Dyke-42	25	10 definite improvement.	X-ray preferred, surgery if refractory.
Kerr-42	2	1 definite improvement.	X-ray is therapy of choice.
TOTAL	128	93 (72%) definite improvement.	

radiation therapy. Hence it is agreed by all that radiation therapy to the pituitary is essential in the therapy of acromegalic patients.

Some investigators claim that there is a decrease in the size of the enlarged osseous structures following radiation therapy. Others claim only decrease in the size of the soft parts. However, it is generally agreed that the progress of abnormal growth is usually stopped by radiation to the pituitary.

Chromophobe Adenomas

Table 3 summarizes the results of various types of therapy of chromophobe adenomas as reported by various authors. Ninety-one, or 51% of a total of 178 patients treated with surgery alone were reported as having obtained definite improvement. Seventy-six, or 59%, of 129 received definite improvement from radiation therapy alone and 136, or 79%, of 172 were definitely benefited by surgery followed by radiation. One point which seems to be clear from this assembled data is that radiation therapy is of distinct benefit following pituitary surgery. Most investigators who have studied this subject will agree that surgical results are improved and that improvement obtained is longer lasting when postoperative x-ray therapy to the pituitary region is applied. All will agree that radiation therapy has little

Table 3
Chromophobe Adenomas

Author Date	Surgery Only No. Cases	Results	Radiation Only No. Cases	Results	Surg. & Radiation No. Cases	Results	Recommendations & Conclusions
Guarini 1925			3	3 definite improve.			
Towne 1930			5	3 definite improve.			Try x-ray 1st, observe 6 mos.
Dyke 1931			4	4 definite improve.			Try x-ray 1st.
Harris 1932			9	6 definite improve.			Try x-ray 1st.
Rand 1935			16	13 definite improve.			Try x-ray 1st.
Pfahler 1935			6	5 definite improve.	4	3 definite improve.	Try x-ray 1st. If no response, surgery.
Dyke 1936			38	10 definite improve.			Try x-ray 1st unless vision poor.
Schnitker	33	25 definite improv.3 yrs.	7	6 permanent improve.	42	42 definite improv. 4 yrs.	Try x-ray 1st unless vision poor.
Henderson 1939	107	45 definite improv.5 yrs.	10	1 definite improve.	80	59 definite improv.5 yrs.	Surgery followed by x-ray best therapy.
Grant 1939	38	21 marked improvement			46	32 marked improve.	Try x-ray 1st, observe 3 weeks.
Sosman 1939			8	7 marked improve.			Try x-ray 1st.
Kerr 1942			23	18 definite improve.			Try x-ray 1st, observe 4 mos.
TOTAL	178	91 (51%) Def.improv.	129	76 (59%) Def.improv.	172	136 (79%) Def.improv.	

effect on cystic chromophobe adenomas and that surgery must be used in these cases. There is some difference of opinion, however, concerning the extent to which radiation therapy should be tried in patients presenting the findings of a chromophobe adenoma. The greatest difference is related to the selection of cases for a trial of radiation therapy. Some authors, especially neurosurgerons working in this field about 10 years ago, believed that surgery was the best treatment and that radiation was of little benefit. Most recent investigators agree that radiation therapy should be tried first if the patient's visual defects are mild, early, and not progressing rapidly. Some believe that if there is no definite improvement in vision a short time following a single series of x-ray treatments, surgical treatment should be applied immediately. Others believe that several series should be given before radiation can be

considered unsuccessful. Many authors do not believe that improvement in vision is necessary to consider the therapy successful. They believe that if the patient does not show any further visual loss, he should be considered as responding favorably and continued as a radiation case. All emphasize the importance of very careful follow-up of the patient by radiologist, neurosurgeon, and ophthalmologist working in close cooperation.

Consideration of the published data collected in Table 3 indicates that from 50 to 60 per cent of chromophobe adenoma patients experience definite improvement following radiation therapy alone. These results are at least as good if not better than those obtained from surgery alone (Table 3). Another point worthy of consideration is the operative risk in pituitary surgery. Cushing's overall surgical mortality was about 5%. In any other hands except a few of the best, the mortality could be expected to be considerably higher. These mortality rates are of considerable importance when compared with practically no mortality following radiation therapy.

Previous reports indicate that about 20% of chromophobe tumors are cystic. This would explain some of the failures in radiation therapy of chromophobe tumors. Most of these cystic tumors would require surgical therapy before improvement could be expected. Many authors report that a large percentage of cases which do not respond to radiation are later found to be cystic at operation. This is a point against not using surgery primarily. On the other hand it hardly seems justified to subject 5 patients to operation to find 1 cystic tumor.

A review of the results of previously published series and consideration of various authors' conclusions suggest that radiation therapy to the pituitary should first be tried in all cases of suspected pituitary adenoma except in those which have severe or rapidly progressing visual defects or other signs of rapid deterioration. When radiation therapy is used first, the patients should be carefully followed for signs of progressive visual loss following adequate radiation therapy so that surgery can be applied before cases which fail to respond become advanced with severe visual loss. Radiation therapy should always be given postoperatively even if preoperative therapy has been given.

Table 4

Cushing's Syndrome
1927-1945

7 Patients treated with x-ray at University Hospitals - 1 male, 6 females. Average age-32 years.

	No. of Patients
Headache at time of therapy....	4 of 7
Visual difficulties mentioned..	2 of 7
Adiposity.....	7 of 7
Absence of menses.....	4 of 5 pre-menopausal females
Hypertension recorded.....	5 of 7
Diabetes mentioned.....	4 of 7
Lethargy and weakness mentioned.....	4 of 7
Slight bitemporal hemanopsia.....	1 of 4 tested
Glucose tolerance decreased....	3 of 6 tested
Sellar changes.....	3 of 7

Results of Radiation Therapy of Cushing's Syndrome

Range of follow-up of 6 cases-2 months to 12 years (1 of 7 patients-incomplete therapy, not included)

Headache..(gone-2, less severe-2)	of 4 with pre-therapy headache
Visual fields..(Normal-1)	of 1 with pre-therapy defect. Worse in one with normal pre-therapy fields.
Generally..(Improved-5, Same-1)	of 6
Return of menses.....	4 of 4
Decrease in weight reported.....	3 of 6
No. dead.(1.unrelated.cause)....	2 of 6
Recurrence of symptoms..... (improved after second series)	1 of 6
No. with no improvement..... (Pa.with adrenal hyperplasia)	1 of 6

CUSHING'S SYNDROME

Seven patients with Cushing's Syndrome (6 female, 1 male) have been treated at the University of Minnesota Hospitals from 1927 to 1945 (Table 4). The average age of this group was 32 years. Four of 7 patients complained of headache, and only 2 of 7 patients complained of visual difficulties at the time of therapy. Four of 7 patients mentioned lethargy and extreme weakness as an especially bothersome symptom. All 7 of the patients were described as being very obese and 5 of the 7 were designated as having trunk obesity only. Menses were absent in 4 of 5 pre-menopausal females and had been absent for a number of years. Hypertrichosis was consistently present in all 7 patients and had been present for about 1 year in most cases. Sparseness of head hair was mentioned in 3 patients, abdominal striae were mentioned in 3 patients, and hypertension was present in 5 of 7 patients. Symptoms of diabetes mellitus were present in 4 of the patients included in this group. Objective examination revealed that no patient had a visual acuity worse than 20/40 in either eye. One patient had a very slight bi-temporal hemianopsia. Some enlargement of the sella or erosion of the clinoids or dorsum was present on 3 of 7 films. An abnormally small sella was present in 1 case. Glucose tolerance was normal in 3 of 6 patients tested and elevated in the other 3. Osteoporosis was reported on 2 of 7 films. Air adrenograms were made in 2 cases. One was reported as positive and the other negative. Surgical exploration of the positive case was carried out and no actual adenoma was found, but hypertrophy of the adrenal was reported. An exploratory laparatomy was carried out in one other case but no adrenal abnormality could be found.

Our data indicates that headache is quite commonly associated with this syndrome. Visual acuity and fields are uniformly excellent. Sellar changes are more frequent than one would expect according to previous reports. Discussion of the frequency of other signs and symptoms would be of no value because this series was assembled on the basis of the frequency of such symptoms in the group and the multiplicity of these symptoms in the individual patient.

All of the patients included in this group except one were treated with 200 ro 220 Kv x-rays and 1 mm. of copper and 1 to 4 mm. of Al filter. The usual dose was equivalent of 900 to 1200 r in air to each of 2 or 3 fields. One patient received the equivalent of only 500 r in air to one field and consequently results in this case cannot be included in judging the effects of x-ray therapy. The last patient treated here received 400 Kv. x-rays to 3 fields - 1200 r in air to each. The results in this case will be presented in detail later.

The shortest follow-up in this series of 6 patients was 2 months and the longest 12 years. Two of 4 patients with pre-therapy headache had less severe headache following therapy and 2 of 4 were completely relieved of this symptom. Visual fields became normal following radiation therapy in the 1 case with a pre-therapy defect. Fields became worse in 1 case with normal pre-therapy field. Weight loss is known to have occurred in 3 of 6 patients. Menstruation has returned with some irregularities in 4 of the 4 patients with absent menses. Five of 6 cases reported marked general improvement such as increase in strength and improvement in well being. The condition of 1 case which was later found to have adrenal hyperplasia on exploration continued to deteriorate.

Two of the 6 patients in this series are now known to be dead. One died 2 months after therapy of respiratory failure during metrazol shock for a manic-depressive psychosis. This case was shown previously at operation to have hyperplasia of the adrenal. No improvement followed radiation therapy in this case. The 2nd case died 8 months after therapy of cellulitis of the hand and arm. There had been considerable general improvement in the interim, however.

The 4 living patients have been followed 3 months, 28 months, 9 years, and 12 years respectively.

Two of the 6 cases received two courses of therapy. One, a 21 year old female, received the 2nd series 3 months after the 1st because the 1st series had produced only slight improvement in her condition. Following the 2nd series, improvement was marked. Menstruation had reappeared after having been absent for 2 years. Headache was absent except during menstruation. The patient's general condition was markedly improved and has remained so for 12 years. She lost some weight and became very energetic and bright in contrast to her previous dullness and lethargy.

The 2nd case, a 15 year old female, received the 2nd series 2 years after the 1st because headache had recurred. This was again relieved by therapy. She lost all excess fat and menstruation appeared even though the patient had never previously menstruated. Improvement was maintained for 9 years. Then the patient began to have complaints the nature of which are not now known. This patient had previously had an adrenal exploration, but no abnormality was found.

The following case report will serve to illustrate the benefits of x-ray therapy to the pituitary in a case of Cushing's syndrome.

Mrs. _____, female, (age 44) was admitted to the University Hospitals on 7-24-44, with a history of marked physical changes One and a half years prior to her admission, she noted rapid increase in weight, puffiness of face, facial hirsutism, obesity of neck and trunk, sudden amenorrhea, a tendency to bruise easily, hypertension to 220 systolic, purplse striae on abdomen, extreme weakness in extremities, dyspnea, orthopnea, and ankle edema. Then some months later she began to lose weight rapidly concomitant with the appearance of polyuria, polydypsia, polyphagia, and glycosuria. At the same time the patient began to have numerous boils and subcutaneous abscesses which required repeated drainage. She was then given daily insulin for her evident diabetes. Admission physical examination revealed a patient typical of classical Cushing's Syndrome. Her blood pressure was 192/100 and her weight was 148. Chemosis and a slight exophthalmous were present. Moist rales were present in both lungs posteriorly. Purpose striae, purpuric marks, and abscess scars were evident. The patient was weak and lethargic. Subsequent laboratory investigation revealed a decrease in glucose tolerance, occasional glycosuria (while receiving insulin), normal air injection adrenograms, possible slight enlargement of sella and slight decalcification of dorsum, enlargement of heart and pulmonary congestion, normal visual acuity and visual fields, and normal BMR. From 8-9-44 to 8-21-44 the patient received testosteron, 25 mg. daily. She also was digitalized and was given insulin with no evident improvement. On 9-25-44 radiation therapy to the pituitary was begun. The patientreported almost immediate improvement in strength. Therapy was completed on 10-11-44. The series of treatments consisted of 1500 r in air total to each of three fields (2 lateral temporal fields and 1 anterior frontal field) delivered with the 400 Kv machine using the Thoreus filter. Total calculated dose to the pituitary itself was 2250 r. Following this, improvement was rapid and remarkable. Dyspnea disappeared, strength increased greatly, purpura disappeared, no further infections developed, symptoms of diabetes disappeared, hirsutism disappeared, body contours changed, medications and diet became unnecessary, all edema disappeared, purple striae faded, and the patient felt much better generally. There was such a remarkable change in the patient's facial contours that she did not appear to be the same person and was not recognized by those who had known her before therapy. The blood pressure recorded 3 months after completion of radiation therapy was 144/94 and her weight was 142. Four months after therapy, menstruation had not yet reappeared. Her only complaint 4 months after therapy was slight pain in the hands, arms, and shoulders. Glucose tolerance had become normal. Follow-up film of sella revealed no change in sella after therapy. When last seen in February 1947, her initial improvements had been maintained. About 1 year after the x-ray therapy she had one period of

menstrual bleeding and once again since then. No regular menstrual bleeding has reappeared. However, the patient has now probably reached her natural menopause.

Our series of cases of Cushing's Syndrome treated with x-ray therapy demonstrates that distinct benefits may be obtained thereby. Perhaps the most beneficial results are alleviation of or complete relief of headaches, improvement in general well being, weight loss, return of menstrual function, ameloriation of diabetes, increased strength, disappearance of skin lesions, and change of appearance towards normal.

This study indicates that a full series of x-ray therapy to the pituitary region is indicated in all cases of Cushing's Syndrome, especially if no adrenal tumor can be demonstrated. Considerable improvement should be expected if the syndrome is on the basis of a pituitary lesion and no damage will be done if the syndrome is on another basis. If there is no response to two courses of radiation therapy to the pituitary, hormone therapy, exploratory laparotomy, or radiation of the adrenals should be considered. It is well known that these patients tolerate surgery very poorly. Consequently at least a trial of a non-surgical procedure would seem to be indicated first.

Table 5

21 Acromegalics treated with x-ray at University Hospital - 11 males, 10 females. Average age - 41 years.

	No. Patients
Headache	13 of 21
Visual difficulties	11 of 21
Visual acuity worse than 20/30 in one or both eyes	5 of 16
Bitemporal hemianopsia	6 of 18
Unilateral temporal quadrantopsia	1 of 18
Sellar changes	15 of 18
Other skull changes	11 of 12

Results of Radiation Therapy of Acromegaly

Range of follow-up of 19 cases - 2months to 11 years (no follow-up - 2 patients)

Headache..(Gone-5, Improved-1, no change-3, unknown-4) of 13 with pre-therapy headache.

Fields..(Improved-4, Same-1, Worse-1, Unknown-1) of 7 with pre-therapy defect (Worse in 1 with normal pre-therapy fields)

Visual acuity..(Improved-2, Same-1, Worse-1)... of 4 with decrease in (Worse in 1 with normal pre-therapy acuity) acuity.....

Generally..(Improved-11, Same-4, Worse-2, Unknown-3)..... of 20 patients.

Number of patients dead..5 of 21 "

Recurrence of symptoms...3 of 12 " with previous improvement after 2, 2, and 12 years.

Number of patients with no improvement... 5 of 17 patients with sufficient follow-up.

Improvement maintained in 7 patients--for $3\frac{1}{2}$ to 11 years.

2 patients followed less than 6 months with no recurrence.

ACROMEGALIC PATIENTS

Twenty-one acromegalic patients (11 male, 10 female) have been treated at the University of Minnesota Hospitals from 1927 to 1945 (Table 5). The average age of this group was 41 years. The range of duration of acromegalic features was 1 to 20 years. Thirteen of 21 patients compalined of persistent headache and 11 of 21 patients complained of some visual difficulty at the time of therapy. Memory difficulties were mentioned by 6, gastrointestinal upsets by 8 and lethargy by 5 of the 18 patients.

Disappearance of menstruation had occurred in 3 of 7 pre-menopausal women. Objective examination revealed the visual acuity to be worse than 20/30 in one or both eyes in only 5 of 16 patients. Six of 18 patients had bi-temporal hemianopsia while 15 of 18 patients had enlargement of the sella turcica or erosion of the posterior clinoids or both. Other skull changes were present on 11 of 12 films.

Our data indicates that the most frequent symptom associated with this syndrome is headache which in most cases is persistent, frequent, and severe. Visual disturbance is also a frequent subjective complaint even though an objective defect in visual fields is less frequent, and an objective decrease in visual acuity is even less frequent. The almost uniform excellence of visual acuity even in the few cases with markedly constricted visual fields is very striking. Fifteen of the patients in this series were treated with 200-220 Kv. x-rays and 1 mm. of Cu and 1 mm. of Al filter. Six were treated with 400 Kv x-rays and a Thoreus filter. The usual dose with the 200 Kv x-rays was the equivalent of 1200 to 1400 r in air to each of 2 or 3 fields. The usual dose with the 400 Kv. x-rays was 1200 r in air to each of 3 ports. Hence the total dosage delivered to the tumor is somewhat higher with the 400 Kv. x-rays.

The advantage of higher kilovoltage cannot be demonstrated by the results of therapy in this series because of the small number of patients treated with the higher kilovoltage. However, it can be stated that the 5 patients of the 6 treated with 400 Kv. x-rays exhibited a good response to therapy.

The shortest follow-up in this series was 2 months and the longest 11 years. Two patients had no follow-up. Following the radiation therapy, 5 of 13 patients with pre-therapy headache were completely relieved of this symptom. Four patients reported no change. The visual fields of 7 patients with pre-therapy field defects were greatly improved in four instances, remained the same in one, and became worse in one. The visual fields in one case with normal pre-therapy fields became worse. Two of 5 with decrease in visual acuity experienced improvement in visual acuity following therapy, 1 of 5 had a decrease in acuity, while 1 with normal pre-therapy acuity was found to have decreased visual acuity after therapy. Eleven of 20 patients reported general improvement following therapy, 4 reported no change, 2 stated that they had become worse, and 3 had no follow-up. One of 2 male patients reported improvement in sexual potency. Improvement has been maintained in 7 patients for from $3\frac{1}{2}$ to 11 years. Two patients with improvement and no recurrence have been followed for less than 6 months. Five of 17 patients receiving radiation therapy only and with sufficient follow-up, showed no improvement of any type.

Five of the 21 patients in this series are now known to be dead. One died during a convulsion 2 months after therapy, 1 died following pituitary surgery at another hospital 2 months after therapy here, 1 died following pituitary surgery at this hospital 5 months after radiation therapy, 1 died following a 3rd laparotomy for pancreatic exploration 1 year after radiation therapy. Necropsy in this latter case revealed no definite adenoma of the pituitary to be present. However, there was an increase in acidophile cells. A 5th case died of an unknown cause 5 years after therapy.

Three of 12 patients had recurrence of symptoms after improvement following radiation therapy. One patient was improved by radiation for about 2 years. Symptoms then recurred and following additional radiation therapy, the patient again improved. A second patient improved for about 12 years by radiation, began to have further indefinite complaints, but received no further therapy. A third patient improved for 2 years by radiation, had recurrence of symptoms and was given additional radiation therapy with no improvement. Five months later the patient's pituitary region was explored but no tumor mass was found. This patient expired postoperatively and a necropsy revealed a reddish soft tumor mass to be present

in the sella. No microscopic diagnosis is available.

One patient continued to become worse after radiation therapy. Surgical removal of a pituitary cyst caused the patient to improve greatly. This patient's history is briefly as follows:

Mr. J , (male) age 29, began to have his first symptoms in 1927. These were vomiting, severe persistent right-sided headache, and beginning enlargement of the hands, feet, face and jaw. In July, 1932, the pituitary region was explored at the Minneapolis General Hospital and a pituitary tumor was discovered which was not removed. X-ray therapy was given at the University of Minnesota Hospitals in January, 1933, with no improvement in the patient's condition. Treatment consisted of 1400 r in air to each of 2 temporal portals with 200 Kv. x-rays. His visual acuity and fields continued to become worse following the x-ray therapy. Headaches and vomiting continued. He had the appearance of a typical acromegalic. His face was enlarged and his lower jaw protruded markedly. His tongue, hands, and feet were greatly increased in size. His fingers were markedly weakened. X-ray film of the skull revealed enlargement of the sella, erosion of the posterior clinoids, and enlargement of the sinuses and lower jaw. Films of the hands showed tufting of the terminal phalanges. Visual fields were generally constricted - most marked in the left eye. There was a paling of the left disc. In view of the failure of the first radiation therapy to relieve the patient's symptoms and prevent eventual blindness, re-exploration of pituitary region was carried out by Dr. Peyton in May, 1933. A pituitary cyst was found, aspirated and completely curetted away. In September, 1933, a second course of x-ray therapy was given through 2 portals - 1430 r in air total to right and left temporal regions each - with 200 Kv. x-rays. Since surgery and the 2nd series of x-ray therapy the patient has improved markedly. Vision has improved especially in the left eye since surgery. The patient has no headaches or vomiting which were present before surgery. In January, 1934, x-ray film of the sella revealed the sella to be slightly smaller than it was before surgery and the dorsum to be somewhat more dense. In December, 1938, the patient had the overbite of the lower jaw corrected with excellent results. He was last contacted in January, 1944, and has had no recurrence of symptoms during the entire 11 year period. Microscopic examination of the biopsy specimen revealed chromophobe adenoma of the tumor not represented in the specimen must have been acidophilic, indicating that the tumor was probably a mixed type.

One patient had an evacuation of a cystis tumor before radiation therapy because of the severe and rapidly progressing deterioration in his vision. There was good improvement in his visual fields and marked improvement in his visual acuity following the combined therapy.

Surgery seems to be indicated in the therapy of acromegalic patients when visual defects are marked and rapidly progressing. Surgical removal of the tumor should always be followed by x-ray to the pituitary.

Our hospital records do not mention any decrease in the size of the acral parts of acromegalics following radiation therapy. It, however, is definitely mentioned that there was no increase in the size of these parts following therapy in 6 of 21 cases. No mention of continuance of growth following therapy is made in any case.

Our series of cases of acromegaly illustrates the fact that survival rates cannot be used to judge the effects of radiation therapy. By considering other points as already mentioned, one can conclude that radiation therapy produces marked improvement in the patient's well being and comfort in at least 50 to 60% of the cases. Improvement when it does occur would appear in most cases to last for an indefinite period. Perhaps the four most beneficial results of radiation therapy in acromegalic patients are alleviation or cure of severe headache, improvement of useful vision when visual defects are present, improvement in general well being, and cessation of growth of

enlarged parts. The following case history illustrates these points:

Miss (. - age 53 - This patient first noted beginning enlargement of her hands, feet, and face in 1932. In 1936 she was first aware of disturbance in her field of vision. Headaches began at about the same time. In February, 1940, when the patient was admitted to the University Hospitals, her appearance was typical of an acromegalic. Skull films on February 1, 1940, showed enlargement of the sella with posterior displacement and thinning of the dorsum sella. However, films of the mandible did not suggest acromegaly while films of the hands did. Visual fields on Feb. 13, 1940, revealed a definite bi-temporal loss. Visual acuity with glasses was normal. In March, 1940, the patient was given a series of x-ray treatment to the pituitary in the amount of 1480 r to each of 3 fields. In May, 1940, the patient was slightly improved. She had less headache and her face felt softer. Her visual fields, however, remained the same. Visual fields on Sept. 12, 1940 again revealed no improvement. Consequently a second series of radiation treatments to the pituitary were given from Sept. 30, 1940 to October 18, 1940. 1480 r were given to each of 3 fields and 660 r to a fourth oral field. Following th s second series the patient experienced further general improvement with complete relief from headaches. However, visual fields on Dec. 12, 1940, March 13, 1941, and June 5, 1941 showed no improvement. On Feb. 2, 1942, visual field studies revealed the fields to be completely normal indicating considerable delay in the response to the x-ray therapy. The patient felt subjectively very well and had no complaints. When the patient was last heard from in Nov. 1946, she reported that the improvement had been maintained and that she was in excellent health.

This case history emphasizes the point that several series of radiation treatments should be tried before resorting to surgery. However, if there is rapid progression of symptoms such as severe rapid loss in vision, surgery should probably be instituted sooner. A patient which does not respond to x-ray therapy may have a cystic adenoma as did one case reported in this series.

Table 6

Chromophobe Adenoma 1927-1945

20 Chromophobe Adenomas treated with x-ray therapy at University Hospitals
9 males, 11 females.
Average age - 45 years.

Diagnosis confirmed by surgery and biopsy..... 11 cases
Diagnosis on clinical basis only..... 9 cases

Surgically Confirmed Cases

Headache..... 8 of 11 patients
Visual difficulties.11 of 11 "
Visual acuity..
(20/200 or worse in one eye-10
worse than 20/30 in both eyes-4
completely normal visual acuity-1)... of 11 "
Fields...
(Bitemporal hemianopsia- 8,
unilateral hemianopsia-3)..... of 11 "
Optic atrophy recorded..... 7 of 11 "
Sellar changes..... 10 of 11 "

Results of Surgical Therapy Followed By Radiation of 10 Chromophobe Adenomas

Range of follow-up of 9 cases-1 month to 8½ years.
(No follow-up-1 patient)

Headache..(Gone-5, Same-1, unknown-1) of 7 with pre-therapy headache
Fields..(Markedly improved-6, slightly improved-1, Same-1, worse-1, malignant, unknown-1) of 10 with pre-therapy defect.
Visual Acuity..(Improved-7, Same-2, worse-1 malignant) of 10 with decrease in acuity.

(Cont.)

Generally..(Improved-8, worse-1 malignant, unknown-1) ..... of 10 patients.
Number of patients dead..... 3 of 10 "
Recurrence of symptoms (headache)..... 1 of 10 "
Improvement maintained in 7 patients..from 1½ to 4 yrs.

CHROMOPHOBE ADENOMA

20 patients (8 male, 11 female) with either clinical or surgically proven chromophobe pituitary adenomas have been treated with x-ray therapy at the University of Minnesota Hospitals from 1927 to 1945 (Table 6). The average age of the entire group was 45.0 years, and the age range was 15 to 70 years. Eleven patients of the entire group were confirmed by surgery and biopsy. Nine patients had a clinical diagnosis only.

The 11 patients with a surgical and biopsy diagnosis will be considered first. Two of 11 cases were found to have cystic tumors on surgical exploration. Eight of 11 of these patients complained of headache at the time of therapy. All 11 of the patients complained of some visual disturbances. Diplopia was mentioned in 3 cases, memory difficulty in 2 cases, and gastrointestinal upsets in 4 of 11 cases. Absence of menses was mentioned in 2 of 5 pre-menopausal females. Hemiplegia was present in 1 of 11 patients. Visual acuity was 20/200 or worse in one eye in 10 of 11 patients. Four of 11 patients had visual acuity worse than 20/30 in both eyes. Marked bi-temporal hemianopsia was present in 8 of 11 cases before surgery. Three of 11 patients had unilateral temporal hemianopsia. Consequently all 11 patients had field defect in one or both eyes. Optic atrophy was present in 7 of 11 patients. Sellar changes were noted on the x-ray films of 10 of 11 cases. A tumor was noted projecting into the nasopharynx on the x-ray film in one case. No case had a completely normal sella or skull on radiographic examination. Glucose tolerance was tested in 3 patients and was normal in all 3. Ten of the above mentioned 11 cases were treated by transfrontal extirpation of the pituitary tumor followed by radiation therapy to the pituitary region usually about 1 week after surgery. Seven cases were treated with 400 Kv. x-rays and Thoreaus filter. The usual dose was 1200-1500 r in air to each of 3 fields. Four cases received 200 Kv. x-rays with 1 mm. of Al. and 1 to 2 mm. of Cu. filter. The usual dose was the equivalent of 1200 r in air to each of 2 or 3 fields. One of the 11 cases had radiation first followed by surgery. This case will be reported in some detail later.

SURGERY FOLLOWED BY RADIATION

Results in the 10 cases treated with surgery followed by radiation are as follows:

The range of follow-up of 9 cases has been 1 months to 8½ years. Headache disappeared in 5 of 7 cases with pre-therapy headache. Headache was the same in 1 case and the results are not known in the other case. Visual fields were markedly improved in 6 of 10 patients with pre-therapy involvement. One patient had slight improvement, 1 had no improvement, 1 became worse, and the condition of 1 is not known. Two of 7 patients with bilateral field defects had bilateral improvement. All of 3 patients with unilateral involvement had improvement. Visual acuity improved in 7 of 10 patients with pre-therapy impairment. In 6 of 10 patients the visual acuity improved from 20/200 or worse in one eye to 20/50 or better. Two such patients had no improvement and 1 continued to become worse. In 1 patient the visual acuity in 1 eye was improved from 20/50 to 20/20. General improvement is reported by 8 of 10 patients. One patient continued to become worse and the remaining case had no follow-up. The one case with hemiplegia was relieved by surgery.

Three of this group of 10 patients are now known to be dead. One died 2 months after surgery after having progressed to complete blindness. This patient had a very extensive, infiltrating and destructive pituitary tumor considered to be the malignant type. The

patient had a high temperature and was in coma immediately before death. Another is known to be dead but time and circumstances are not known. A third died of a septicemia $8\frac{1}{2}$ years after surgery.

Recurrences have been very uncommon. In 1 of these 10 cases headache returned after 3 years. No further therapy was given. This is the patient that expired $8\frac{1}{2}$ years after surgery. Seven patients have been followed from $1\frac{1}{2}$ to 4 years and none of these have had recurrence of any kind.

This study indicates that in confirmed cases of pituitary chromophobe adenoma headache, visual complaints, decrease in visual acuity, defective visual fields, and optic atrophy are almost universally present. Other complaints are much less frequent. Sellar changes demonstrated on x-ray film are also present in practically all cases.

Surgery followed by radiation therapy in these cases has been shown to produce marked and lasting improvement in headache, visual fields, visual acuity, and general well being in the majority of patients.

The following caae history will illustrate a cystic tumor showing no permanent response to radiation therapy alone but followed by lasting response after 2 craniotomies and radon implantation.

Mr. ____ (male) age 35 - first noted some difficulty in coordination and visual depth perception and constriction of visual fields in Oct. 1941. He also complained of occasional headache and some diplopia. Specific condition and therapy arranged chronologically were as follows:

Feb. 26, 1942
Bi-temporal upper quardranopsia. Normal visual acuity.

Mar. 2, 1942
Skull films were negative except for soft tissue mass in sphenoid sinus.

Mar. 9, 1942 to
Mar. 24, 1942.
1200 r in air given to each of 3 fields. (2 lateral and 1 anterior, 300 r thru oral cone. 220 Kv. with 1 mm. al and 1 mm. cu. filter).

June 9, 1942
Soft tissue mass still present.

June 16, 1942
No improvement. Visual fields the same. Visual acuity still normal.

June 17, 1942
Evacuation of a cystic chromophone adenoma thru transfrontal craniotomy. Biopsy - chromophobe adenoma of pituitary.

June 24, 1942
Soft tissue mass smaller.

June 25, 1942
Visual fields normal. Visual acuity normal. Marked general improvement.

Dec. 1942
Blurring of vision and limitation of fields reappeared.

Mar. 29, 1943
Soft tissue mass larger.

Mar. 29, 1943
Marked bi-temporal hemianopsia. Visual acuity RE 20/20 LE 8/400

Mar. 31, 1943
2nd evacuation of pituitary tumor with insertion of 2.9 mc of radon in pituitary fossa.

Apr. 7, 1943
Soft tissue mass the same.

July 7, 1943
Practically normal visual fields. Visual acuity both eyes 20/20.

May 24, 1946
Improvement maintained. Visual fields almost normal. Several convulsions since Dec. 1945.

Table 7

Chromophobe Adenoma 1927-1945

	No. of Patients
Headache	6 of 9
Visual difficulties	9 of 9
Visual acuity worse than 20/30 in one or both eyes	2 of 5 tested
Fields.. (Bitemporal hemianopsia-6 (Unilateral hemianopsia-1)	of 7 tested
Optic atrophy recorded	4 of 9
Sellar changes	5 of 6

Results of Radiation Therapy Alone in 9 Clinical Chromophobe Adenomas

Range of follow-up of 8 cases- $2\frac{1}{2}$ to 12 years (no follow-up- 1 patient)

Headache..(Gone-4, Same-1, unknown-1).... of 6 with pre-therapy headache.

Fields..(Markedly improved-2, slightly improved-1, same-1, unknown-3) of 7 with pre-therapy defect.

Visual Acuity..(Improved-0, worse-4, unknown-1) of 5 with recorded visual acuities.

Generally..(Improved-7, no improvement-1, unknown-1).... of 9 patients.

Number of patients dead.....2 of 8 patients followed.

Improvement maintained in 6 living cases...from 3 to 12 yrs.

CLINICAL CHROMOPHOBE ADENOMAS TREATED WITH RADIATION ONLY

Nine patients were treated with radiation only (Table 7). Six of these complained of headache at the time of therapy. The status of the other 3 is not known. All 9 patients complained of some visual difficulties. Diplopia was mentioned by 2 patients, adiposity by 2 patients and hemiplegia by 1 patient. Two of 6 pre-menopausal women were amenorrheic and 1 of 3 males mentioned decrease in potency. Visual acuity was worse than 20/30 in both eyes in 2 of 5 patients with recorded visual acuities. Visual acuity was worse than 20/200 in one eye in 1 of 5 patients. Three patients had normal visual acuities. Bi-temporal hemianopsia was present in 6 of 7 patients and unilateral hemianopsia was present in one case. In 4 of these cases the defect was marked. Optic atrophy was present in 4 of 9 patients. Enlargement of the sella was demonstrated in 5 of 6 patients by means of x-ray films. The glucose tolerance was decreased in 2 of 2 patients tested.

Eight of these patients were treated with 200 to 220 Kv. x-rays with 1 mm. of Cu. and 1 to 3 mm. of Al. filter. The usual dose was the equivalent of 1200 to 1500 r in air to each of 2 or 3 fields. One patient was treated with 400 Kv x-rays.

The range of follow-up of 8 of these 9 patients was $2\frac{1}{2}$ to 12 years. Four of the 6 patients with pre-therapy headache had complete relief of headache. In 1 case the headache remained the same and the status of 1 case is not known. Visual fields were markedly improved in 2 of 7 patients with pre-therapy involvement. One of 7 patients had slight improvement while 1 remained the same. The condition of the remaining 3 is not known. Visual acuity was not improved in any case. In 4 of 5 cases with pre-therapy visual acuity recorded, visual acuity actually became worse. In 1 case the post-therapy status is not known. Seven of 9 patients claimed general improvement while 1 of 9 claimed no improvement. There was no follow-up in 1 case. Hemiplegia disappeared almost completely in the 1 patient involved. One of 2 women with amenorrhea experienced reappearance of menstruation. The other patient was past the menopause before therapy was given.

Two of these 9 patients are now known to be dead. One died $3\frac{1}{2}$ years after therapy of an unknown cause, after having had some initial improvement in

general well-being. The other died 2½ years after therapy was completed, after having been semi-conscious for 8 weeks. There was no definite improvement in this case following therapy, which consisted of three complete series of radiation to the pituitary at 6 month intervals.

The following case history illustrates the benefits of radiation therapy alone in a clinical case of chromophobe adenoma.

Mr. ... (male) age 49 - was admitted to the University of Minnesota Hospitals on 4-19-40 with the complaints of weakness, irritability, depression, nausea, vomiting, abdominal pain, impotence, occipital headaches, lethargy, left-sided weakness, and diplopia. Physical examination revealed his blood pressure to be 140/90. The right pupil was larger than the left. There was a moderate weakness of the entire left side of the body with a decrease in sensation on the same side. BMR and glucose tolerance test were normal. Visual acuity was 20/25 in each eye. The visual field of the right eye was normal while the visual field of the left eye was greatly constricted. X-ray film of the sella revealed it to be considerably enlarged. The posterior clinoids and dorsum were atrophic. The clinical impression in this case was extensive chromophobe pituitary adenoma with pressure on the cerebral peduncles. The patient was advised to have pituitary surgery but refused surgical exploration. Consequently in May, 1940, a series of x-ray treatments were given to the pituitary thru 3 ports with 1200 r in air to each port at 220 Kv. About 1 month later the patient claimed great improvement. Auditory and visual hallucinations which had been present previous to x-ray therapy had disappeared. Memory and concentration had improved greatly. He claimed some improvement in vision. However, visual acuity was the same, but the visual fields of both eyes were constricted to a greater extent than they had been. Only 10° of central vision remained in the right eye. His headaches persisted. By Oct. 1, 1940, the visual field of the right eye was even more constricted, but the left eye remained the same. Consequently a second series of x-ray treatments similar to the 1st were given in October, 1940. In Dec. 1940, the patient claimed subjective improvement. He stated vision had improved. He continued to be impotent. He had developed a tremor and his left side continued to be weak and lacking in normal sensation. His visual acuity remained normal and his fields were the same. In March, 1941, his headaches, nausea, and vomiting were still present. The weakness of the left side persisted. His visual fields remained the same, but the visual acuity in the left eye had decreased to 20/50. Skull film on March 21, 1941, revealed definite evidence of recalcification of the sella. In April, 1941, he was given a 3rd series of x-ray treatments to the pituitary similar to the 1st 2 courses. In April, 1941, he reported less severe headache. His visual fields remained about the same. The patient was then not seen again until February, 1945, at which time he reported remarkable improvement which had begun in July, 1942. His headaches disappeared completely. His memory was normal. The tremor and hemiplegia disappeared so that he could walk normally. In September, 1942, he took a job as a night watchman. Nausea and vomiting were absent. Visual fields recorded in February, 1945, revealed the right eye to be completely normal while the left eye had improved to a 30° vis al field. Visual acuity in the right eye was normal and in the left was 20/200. Strength of the left side was practically normal. The patient seemed to have been completely rehabilitated and was very happy over the outcome.

Analysis of these cases treated with radiation only, indicates that there is considerable relief of headaches and considerable general improvement in a majority of the patients. In all of the patients trested with both pre-and post-therapy visual fields, there was either an arrest of the continuous advance of the field defects or an actual improve ment in the visual fields. Some investigators such as Dyke and Davidoff[33] contend that an arrest of an advancing field defect with no actual improvement should be considered as a therapeutic success. In cases with a gradually progressing field defect of long standing, considerable irreversible damage to the optic apparatus can be expected.

In such a case even complete surgical removal of the offending tumor would not be expected to produce any remarkable improvement. Hence an arrest of the progress of the defect would indicate that at least further growth of the tumor had been inhibited by the therapy.

It is also noted that in all of the patients tested, the visual acuity has become worse following radiation therapy. In only one case is the visual acuity considerably worse. In the others the decrease in visual acuity following therapy is slight and could well be explained on the basis of refractive errors due to the advancing age of the patient. However, the one case with considerable decrease in visual acuity suggests some growth of the tumor following radiation therapy.

From the series it would appear that the best results in chromophobe pituitary adenomas are obtained with surgery followed by radiation rather than by radiation alone. However, in only two cases was more than one series of treatments given. One of these showed no improvement suggesting the possibility of a cystic tumor. This patient should have had surgical interference after radiation alone was found to be ineffective. The second case, whose history has already been presented in detail, demonstrates that repeated series of radiation to the pituitary may finally produce the desired results. Our series suggests that chromophobe tumors probably require a larger dose of x-ray than do the acidophil tumors. Probably several series of treatments are necessary for most chromophobe tumors while one series appears to produce the desired results in most acromegalic patients.

If a patient's visual fields and acuity are not greatly affected when first tested and the defects are not rapidly advancing, radiation therapy should probably first be tried. However, it should be emphasized that such a course depends upon close cooperation between the radiologist, neurosurgeon, ophthalmologist, and patient. Very frequent and active follow-ups would be necessary to detect rapidly progressing visual defects which would necessitate surgical intervention. In any case the neurosurgeon should see the patient before radiation therapy is begun so that he may have an active part in selecting the cases for either surgical or radiation therapy.

CONCLUSIONS

Cushing's Syndrome

From reports by other authors:

1. Patients with Cushing's Syndrome are poor surgical risks. Hence at least a trial of non-operative therapy is indicated.
2. Radiation of the pituitary is the treatment of choice. Remarkable, complete cures have been produced by this method.
3. Hormonal therapy and radiation of the adrenals may also be tried if there is no response to radiation of the pituitary.
4. If adrenal hyperplasia or tumors are suspected or can be demonstrated on adrenograms, adrenal surgery may be of benefit. Adrenal changes apparently may be primary or secondary to a pituitary tumor.
5. Pituitary surgery may be indicated if visual changes and skull films suggest the presence of an actual tumor and the patient has not been relieved of endocrine symptoms by other therapy.

From the University Hospital series:

1. Radiation of the pituitary has produced remarkable complete cure in several cases with Cushing's Syndrome and has produced some improvement in most of the others treated.
2. Several series of x-ray therapy may be necessary to produce the desired results.

Acromegaly

From reports by other authors:

1. Radiation therapy of the pituitary is the treatment of choice in acromegaly. Definite lasting improvement in vision and endocrine symptyms is obtained in a large percent-

age of cases.
2. There is at least an arrest in the growth of the acral parts following radiation.
3. Acromegalics are frequently poor surgical risks. Hence surgery should be avoided unless there are severe or rapidly progressing visual defects. Then surgery is indicated.
4. Surgical removal should always be followed by radiation because surgery may relieve visual symptoms but not endocrine changes.
5. Radiation therapy of acidophilic adenomas is more frequently followed by favorable response than is the case with chromophobe adenomas.
6. Patients who do not respond to radiation may be found to have cystic tumors. This is not always the case.

From the University Hospital Series;

1. Marked lasting improvement is produced in the majority of acromegalic patients by radiation of the pituitary.
2. Surgery may be indicated if visual loss is severe.
3. Cases which do not respond to x-ray may be found to have cystic tumors.

Chromophobe Adenomas

From reports by other authors:

1. The highest percentage of improvement and the most prolonged improvement is obtained in patients treated with surgery followed by radiation. The combined therapy is better than either method used alone.
2. Cystic tumors do not respond to radiation.
3. Good results can be obtained with radiation alone in solid tumors, but the percentage of patients benefited is not as great as the percentage of acromegalics benefited.
4. Radiation alone should be given a trial first unless vision is markedly defective or the defect is rapidly progressing. The patient and especially his visual fields should be carefully followed.
5. If x-ray does not produce the expected results (varying somewhat from author to author) surgery should be used.
6. The chief concern in deciding whether to use surgery or x-ray is the preservation or improvement of the patient's vision.
7. X-ray should always be used postoperatively in every case whether used preoperatively or not because it decreases the percentage of recurrences, and improvement is maintained for a longer period.

From the University Hospital series:

1. Surgery followed by radiation has produced marked prolonged improvement in a large percentage of cases.
2. Results from radiation alone have not been as good perhaps because adequate therapy was not given. Several series may be necessary. Chromophobe tumors appear to require a larger dose to produce the desired results than do the chromophile tumors.
3. Radiation alone should be tried:
   a. When the patient refuses surgery or when the patient is not a good surgical risk for other reasons.
   b. When an expert neurosurgeon is not available.
   c. When visual defects are very slight.
   d. When visual defects are not rapidly progressing and there is no immediate danger of considerable loss of remaining useful vision.
4. Surgery is indicated:
   a. When visual defects are marked. Slight swelling of the tumor following radiation might produce complete loss of useful vision in such a case.
   b. When visual loss is rapid and has appeared suddenly.
   c. When adequate radiation fails to produce improvement in vision or fails to stop the advance of visual defects. The results of radiation therapy should be closely checked by the radiolo-

gist, neurosurgeon, and ophthalmologist working in cooperation. Visual fields and acuity should be carefully followed very frequently and in some cases even at weekly intervals.

5. The neurosurgeon should see the patient before therapy is begun even if x-ray therapy is to be used.

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III. RESULTS OF SURGERY AND RADIATION FOR CARCINOMA OF THE BREAST WITH AXILLARY METASTASIS

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Is postoperative roentgen irradiation of value for carcinoma of the breast? This question has been raised repeatedly and the answers have varied. There seems to be only one method available to attempt an answer, and that is by means of statistics.

The difficulty with the statistical method is that so many variables enter in and it is always a question if one or more of these variables are weighed. The problem is to obtain normal samples.

The results from any therapy method differ tremendously with the stage of the disease. When a single freely movable mass in the breast is the only involvement of cancer found during a radical operation, surgery alone is very likely to result in a cure; and the patients in this group are, therefore, not suitable for a comparison. It is very doubtful that radiation would contribute anything to the survival in this group. When the disease is more extensive the results are less satisfactory, but comparisons are still difficult. A more specific criterion is needed and the one most usually adopted and the one probably most suitable and objective is involvement of axillary nodes as established histologically.

Another problem of special importance is the measure of results obtained. If the criterion "clinical cure" is used, then it depends upon how carefully the patient is examined (e.g., x-ray films of chest and bones), and that is an unreliable factor. The cause of death is another term which may be used erroneously. Therefore, it seems advisable to use the uncorrected 5-year survival figure as a measurement of results, or still better, the survival curve. The assumptions then made are that deaths from other causes than cancer of the breast would have similar statistical distribution just as is made for other factors; such as, age, spread of the

disease, etc.

It is evident that the results will depend upon the methods of treatment and how skillfully they are carried out. This refers with equal consideration to the surgical and the radiological methods employed.

In a previous piblication, the results obtained in all patients with carcinoma of the breast referred for x-ray therapy between the years 1926 and 1938 to the radiation therapy section at the University of Minnesota Hospitals have been discussed. At this time a study has been made of a selected group.

All patients who fulfilled the following criteria were included in this group:

(1) Had axillary node involvement at the time of operation proven by microscopic examination.

(2) Had no known distant metastases at the time of operation (lungs, liver, bones, etc.).

(3) Had postoperative roentgen ray therapy instituted within 32 days or less. The majority of patients were treated 10-14 days following operation.

(4) Had radical mastectomy performed at the University of Minnesota Hospitals. It may be mentioned that these patients were operated upon by a number of different surgeons, some of whom had limited experience.

Analysis of Cases

Of all patients treated from Jan. 1, 1927 to Jan. 1, 1942, 110 fulfilled the aforementioned criteria. Records of those treated after 1941 were not studied as a 5-year survival could not be determined after that date.

Survival was computed from the date of operation. Untraced patients were considered to be dead as of the date of the last recorded information. Fortunately, it was possible to trace all but one patient at least 5 years or until death.

The youngest patient was 24 years and the oldest 79 years old. The ages according to decades are given in Table 1. The median age was 51 and the average age 50.8 years. One male patient is included in this series.

Table 1

Age Incidence According to Decades	
Age	Number of Patients
20 - 29	3
30 - 39	16
40 - 49	28
50 - 59	37
60 - 69	21
70 - 79	5

Results

In our series of 110 cases, 45 or 41% survived 5 years or longer. Of these patients, 37 or 34% may be classified as "clinically cured" for 5 years, as 8 or 7% were alive with recurrences. Table II presents the results in detail giving the number of patients treated each year and the per cent surviving one, two, three years and so on up to 15 years following the operation.

The normal mortality rate for this average age (50) in five years is about 8% and in ten years 19%.

It has usually been considered that a radical mastectomy should be performed only when there seems to be a reasonable chance of removing all the cancer cells. Different criteria have been been adopted by different surgeons. The only restrictions used here are: (1) The general condition of the patient prevents major surgery; (2) Distant metastases are definitely found; this includes unquestionably involved supraclavicular nodes; (3) Axillary nodes are fixed; (4) Inflammatory carcinoma; (5) Carcinoma present after fifth month of pregnancy.

No patients have been excluded from this series because of questionable operability, but serious consideration

Table II

Survival of Patients with Carcinoma of the Breast with Axillary Metastases Receiving Roentgen Therapy Following Radical Mastectomy

Year	No. of Cases	Number of Years														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1927	1	1	0													
1928	2	2	1	1	1	1	1	1	1	1	1	1	1	1	0	
1929	4	3	3	3	1	0										
1930	5	2	1	1	0											
1931	5	5	4	3	3	3	3	3	3	3	2	1	1	1	1	1
1932	5	4	3	2	1	1	1	1	1	1	1	1	1	?		
1933	12	8	7	6	5	5	4	4	4	4	2	2	?			
1934	11	10	8	6	5	5	5	4	4	3	3	2	?			
1935	8	7	5	5	5	5	4	4	3	3	3	?				
1936	2	2	1	1	1	0										
1937	3	3	3	2	2	2	2	?								
1938	7	7	6	4	3	3	3	2	?							
1939	16	16	12	11	11	9	?									
1940	16	14	10	9	8	7	?									
1941	13	10	10	8	5	4	?									
Total	110	110	110	110	110	110	65	53	53	53	53	45	22	17	17	17
Living		94	74	61	51	45	23	17	16	15	12	7	3	2	1	1
Percentage Living		85	67	55	46	41	36	32	30	28	23	15	14	12		

was given to the advisability of including 10 of the cases. In 3 of the 10, the radiologist reported possible or probable lung metastases prior to operation. One of these patients lived 3 years, but the other two died within 3 months after the operation. The exact cause of death was not known in two of the cases, but the third one who lived only 3 months was known to have died of metastatis carcinoma. Five had local excision of the mass in the breast one to six weeks before they were referred to the University Hospitals for radical mastectomy for purpose of biopsy or under the impression it was benign. One had simple mastectomy about one month previous to the radical mastectomy; and in one patient, metastases, which could not be removed, were noticed under the clavicle at the time of operation.

None of these 10 patients survived five years. If they were excluded from the series, the 5-year survival would be 45%.

Our group of those having local excision prior to radical mastectomy is too small to have any statistical significance, but Harrington[1] in reporting a large series of carcinoma of the breast at the Mayo Clinic states:

"The poorest surgical results in carcinoma of the breast are obtained from secondary radical amputation after primary partial removal of the tumor. In approximately 10% of the cases in which radical amputation has been performed at the Mayo Clinic, a minor operative procedure had been performed elsewhere one month or more prior to coming to the clinic. In this group, involvement of lymphatic structures had occurred in 74% of cases as compared with 63% of cases in which primary radical operation had been performed. The results of secondary radical amputation are correspondingly less satisfactory than those of primary radical amputation."

Adair[2] condemns the procedure and also reports poorer results in such cases stating that:

> ...of the 283 cases classified as 'operable after local excision' there was a 5-year salvage of only 53 cases, representing 20 per cent. Had the patient been properly handled at the beginning she at least would have had a 51% chance of 5-year cure.

In Table III, statistics from some of the larger clinics are presented for comparison. These were particularly chosen from the literature because they reported their statistics as 5-year survivals* rather than as "clinical cures," and all their cases presented in the table had metastases to axillary nodes as proven by histological examination.

It has previously been shown that the clinical judgment of axillary metastases is a highly fallible procedure. In our series, 76 or 70% had palpable axillary nodes and 33 or 30% did not have palpable axillary nodes but all had involvement histologically.

In one patient there was no mention of an examination of the axilla. Of those who had palpable axillary nodes the 5-year survival rate was 43%; and of those who did not, the survival rate was 36%.

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*Haagensen and Stout in giving their five-year results of radical mastectomy in primary cases report 36.17% alive, without recurrence 5 years after operation and 5 2% alive with recurrence five years after operation or total 41.4% alive at the end of five years. In reporting their cases with axillary node involvement, they report the results as 5-year clinical cures. We have taken the liberty of applying the proportion 36.2 : 41.4 to their 5-year clinical cures in order to express their results in this group as 5-year survivals. They report 24.7% 5-year clinical cure for those with axillary node involvement treated by radical mastectomy only, and 31.5% 5-year clinical cure for those who had postoperative prophylactic radiation plus radical mastectomy. The adjusted figures for the above two groups are 28.2% and 36% respectively.

Haagensen and Stout[3] reported that in 325 cases in which axillary nodes were not palpable clinically, 143 or 44% microscopically had axillary metastases. In 278 cases in which axillary nodes were thought to be involved by clinical examination 236 or 84.9% had microscopic evidence of metastases - an error of 15.1%. Hooper and McGraw[4] found that in 145 cases with palpable axillary nodes 11 or 76.5% had demonstrable metastases (error 23.5%). In 97 cases with no nodes palpable on clinical examination, metastases were later demonstrated in 38 or 39%. Simmons, Taylor and Welch[6] in their clinical appraisal of axillary involvement, noted that in 61 cases in which nodes were found on physical examination positive

Table III

Comparative Statistics in Cases with Axillary Metastases Proven by Histological Examination

Author	Year	No. of Cases with Radical Mastectomy Only	% 5-year Survivals	No. of Cases with Radical Mastectomy Plus Post-op. Radiation Therapy	% 5-year Survivals
Harrington	1910-1935	732	24.3	201	29.4
Haagensen & Stout*	1915-1934**	154	28.2	143	36.0
Jessop[5]	1923-1932	96	30.5		
Hooper & McGraw	1918-1935	55	21.8	94	31.9
Stenstrom & Baggenstoss	1927-1941			110	41.0

** Many of radiated patients treated after 1923

evidence of carcinoma was demonstrated in 53 or 87% on microscopic examination; and in 79 cases in which no axillary nodes were felt, carcinoma was found on dissection of the axilla in 37 or 46%.

In 36 of the 110 cases, radon seeds were used and in one case 1960 milligram hours of radium. The amount of radon used varied from 1267 to 4360 millicurie hours, but in the great majority of cases approximately 4000 millicurie hours was employed. The above 37 cases comprise the great majority of cases treated from 1931 to the middle of 1936, there being only two cases treated with radon after that. The radon seeds were implanted over the intercostal spaces and in the axilla, the exact location depending upon where the surgeon believed it would be of most benefit. Of these cases, 16 or 43% survived 5 years or longer.

Complications

Irradiation sickness was not an infrequent occurrence, but we do not have any statistics regarding its frequency in our series. In no case was it severe enough to necessitate the cessation of therapy or reduce the total dose.

In three patients radiation lung fibrosis was reported by the radiologist after x-ray examination. In one of these patients, it was also reported that there were changes in th 2nd, 3rd, 4th and possibly 5th ribs on the right which might be accounted for by radiation necrosis. This same patient also had an ulcer at the apex of the scar in the right axilla which was attributed to radiation therapy. This ulcer was later excised and skin grafted with good results. None of these patients complained of any distress referrable to radiation lung fibrosis. Two of these patients lived over 5 years (10 and 6 years) and one died 2 years after operation.

One patient developed a severe derma-

titis of the case, neck, anterior chest wall, arms and hands which was diagnosed as x-ray dermatitis by the dermatologist although this patient gave a history of similar, less severe dermatitis previous to therapy.

Technique of Therapy

For the period covered by this stidy (1927-1941 inclusively) only two important changes occurred in the technique of postoperative roentgen therapy.

The majority of patients were treated from 10-14 days following the radical mastectomy, and the following physical factors were employed: 200 kvp, 30 ma, 0.5 mm. Cu and 1.0 mm Al filter (H.V.L. 0.9 mm. Cu), focal skin distance 70 cm.

During the period 1927 to August, 1938, which included 56 patients, approximately 250 r (in air) was given every other day for four treatments (total about 1000 r). This was directed to a field which included the anterior breast region, parasternal line medially, anterior supraclavicular cervical and axillary regions. The series was to be repeated in about 2 months, but some patients did not cooperate in this respect. After 1928 additional treatments were administered to the axilla and the supraclavicular region.

From August, 1938, through 1941, which included 54 cases, about 220 r (in air) was given every other day for six treatments (total about 1300 r) anteriorly to a field which included the above mentioned region. At the same time a treatment was directed to the supraclavicular or axillary region, alternating these two fields with each anterior field. Four treatments of approximately 300 r (in air) each (total about 1200 r) thus was administered to the supraclavicular and axillary regions in addition to what was given in the anterior field. A second series was not given under this plan.

Of the 56 patients treated during the period 1927-1928, twenty-one or 37.5% survived 5 years or longer and of the 54 patients treated after the change in therapy 24 or 44.4% survived 5 years or longer.

Present Technique

After 1941 the technique was again changed, and at present six treatments are administered to the large anterior field using 140 kvp, with 1.0 mm. Al and 0.25 mm. Cu filtration (H.V.L. 0.56 mm Cu), focal skin distance 70 cm. 200 r (in air) is given at each treatment (total 1200 r in air). The breast area also received two tangential fields, from a lateral and medial direction, of 300 r (in air) to each employing 200 kvp, 1.0 mm. Al, 0.5 mm. Cu filtration (H.V.L. 0.9 mm Cu) focal skin distance 60 cm. The axilla and supraclavicular areas are treated alternately with the above mentioned anterior and tangential fields with 300 r (in air) per treatment, total 1200 r (in air) to each. The latter mentioned physical factors are used for these areas. Treatments are given every other day, the entire series extending over a period of sixteen days.

As yet no figures are available for patients treated with this technique.

Summary

Table III gives a collection of representative statistics, of the 5-year survival for carcinoma of the breast with axillary metastasis. It shows that radical mastectomy with modern technique as a rule produces less than 30% 5-year survival. The addition of post-operative x-ray therapy has consistently increased the survival rate according to the figures in the table. The increase is not large, but the fact that it is consistent indicates definite advantage of post-operative irradiation.

The argument has been used that a full cancericidal x-ray dose can not be delivered to a large field overlying the lung and that it, therefore, is useless to apply radiation. It must, however, be remembered that some carcinomas are destroyed with a much smaller dose than what usually is considered lethal and that only small foci of cancer cells are present after the surgery. The statistics also seem to bear this out. The method of therapy is, however, of great importance and it is doubtful that anybody as yet has discovered the most

suitable volume and time distribution of the radiation. The fact that better results were obtained in our series after the method had been changed (from 37 to 44%) may be an indication that it was improved and holds out hope for still better results in the future. It is, of course, possible that improved surgical method should be given part of the credit.

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IV. GOSSIP

At the annual meeting of the Minnesota Cancer Society in St. Paul, Saturday, March 8, Drs. L. G. Rigler, O. H. Wangensteen, and John J. Bittner were elected to the Board of Directors. The Society reported collections of $230,000 in 1946 and a proposed collection of $225,000 in 1947. The national drive for funds is for $12,000,000, of which Minnesota's share is 2 per cent. The special feature of the meeting was the donation of $75,000 for the building of a cancer research institute at the University of Minnesota. For some time it has been apparent that government, foundations, and individuals were interested in giving money for research projects but not for research buildings. It has been our experience that when space in a building is provided that it is much easier to build a program. Minnesota has obtained many research grants in the past, and we have one of the outstanding research teams in the country. A place to house this group will attract more project money and more graduate students interested in cancer research. Arthur H. Wells, M.D., first Vice President of the Cancer Society, Chairman of the Minnesota State Medical Association Cancer Committee and Pathologist, St. Luke's Hospital, Duluth, was the author of the motion to make the grant. He received fine support from both lay and professional people, and the opinion was unanimous that the grant should be made. The Society hopes to raise a sufficient sum this year to make a second gift of $75,000 in 1947, and the same for the succeeding years, 1948 and 1949. If construction should be started on the unit which will consist of two floors in the Mayo Memorial Building, undoubtedly a loan could be obtained if the complete sum had not been raised at the time. At the cancer meeting we learned of the small amount of money which is devoted strictly to cancer research. Last year the American Cancer Society and the government set aside $5,000,000 to be earmarked for cancer research. At the same time, $21,000,000 was spent for animal diseases and $7,000,000 for white pine blister research. Another comparison was the amount of money spent for dog medicine, - exactly $5,000,000. Cancer research has a long way to go, involving as it does, the fundamental concepts of life. The spade work in the field will take years and the problem is not to be compared with the billions which the government spent on atomic research, which, after all, was in the field of applied research as the background had been developed. Other cancer projects are detection centers for the examination of the apparently well and those with minor complaints, nursing service (education and care of patients), courses and booklets of instruction, etc. On Thursday, March 6 I was in Chicago at the annual meeting of the American Cancer Society which has an ambitious program for the coming year. Proposals include a new cancer journal, new movies, greater allotment of research money, hiring health educators for state units, and further expansion of the detection center idea. In a real detection center, a group of apparently normal individuals are given periodic physical examinations with the hope of finding a certain number of asymptomatic malignant tumors. (The variation of this theme is to examine individuals with suspicious complaints.) In each case the medical society approves the center and cooperates in the project. There was more discussion on this point than any other. Some observers felt that the idea was too expensive, but no one knows how much it would cost because it never has been tried. In case-finding in tuberculosis, somewhere between $3,000 and $4,000 is necessary to detect each case according to some reports. Many physicians feel that the detection center idea is a challenge to their types of examination, to which the Cancer Society replies, "the average patient who presents himself to a physician without any complaint finds it difficult to obtain an examination". The Kansas Medical Society on the other hand had pledged itself to give such examinations in doctors' offices. They have adopted an official blank and will make their report to a central agency. It appears this problem is far from solved, but it is certain it cannot be solved by argument and name calling. It would be ideal if medical schools would set up such centers and teach medical students this method of examination so they would be able to do these examinations when they go into practice.....