1956

Hypophysical surgery for metastatic carcinoma of breast

Stanley E. Pollman
University of Nebraska Medical Center

HYPOPHYSIAL SURGERY FOR METASTATIC CARCINOMA OF THE BREAST

Stanley Eugene Pollman

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 2, 1956

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

The purpose of this paper will be to present the methods used in destroying the hypophysis and to evaluate their effect upon metastatic breast carcinoma. The ablation of this gland brings about important physiologic changes in the human organism and these will also be discussed. Five patients have undergone hypophysial radon seed implantation at U.N.H. and a critical analysis of these cases will be included.

Experimental hypophysectomy in dogs was first carried out successfully by Cushing (1) in 1910. The dogs all died within a few days to three weeks and he felt the pituitary is essential for life. The first hypophysectomy in man was apparently performed by Lisser (2) in 1944 for a case of Cushing's disease. Pattison and Swan (3) have the first recorded record of implantation of radon seeds in the pituitary, also for Cushing's syndrome in 1938. In the earlier cases, mortality and morbidity rates were high. The endocrinology of the gland and its effect on the target organs wasn't understood and many died of hormonal deficiencies.

In the past few years, hypophysectomy has been performed more frequently, since the availability of

ACTH and Cortisone. This has made succesful recovery from the procedure more easily obtainable.

The effect of removal of the pituitary on the growth of carcinoma was first studied by Ball (4) in 1932 with his experiments in rats. A group of hypophysectomized albino rats underwent mammary carcinoma transplants. He noted that the rate of tumor growth was markedly reduced in relation to a group of controls, although there was not complete cessation. He also ran a series in which the tumor was first transplanted and allowed to grow. Hypophysectomy was then performed and there was an immediate retardation in the rate of growth. They postulate that this result may be due to the removal of some hormone elaborated by the pituitary. A year later a British group (5) performed the same experiment and obtained similar results. However, they felt that the retardation of tumor growth was a consequence of cachexia following hypophysectomy. In 1939 Korteweg and Thomas (6) transplanted mammary tumors on to hypophysectomized and control mice and stated the only difference was slowed rate of growth in the former group. They suggest that the difference in the two groups is entirely quantitative rather than qualitative. Maurik (7) transplanted mammary gland carcinoma on to successive numbers of hypophysectomized mice. The rate of growth

was significantly reduced in relation to controls. The rate of retardation didn't change after repeated transplantation. Loeffler (8) transplanted fibrosarcomas, with no difference in percentage of sucessful grafts and concludes the hypophysis is not necessary for successful growth of this type of tumor. Gardner (9) and Agate (10) were of the same opinion. Neither could Nagareda (11) demonstrate any hypophysial effect on the development of lymphoid tumors. However, most investigators (12, 13, 14, 15), in recent experiments feel that the pituitary has a definite effect on neoplastic growth in their studies.

A Stanford group (13) fed an Azo dye compound (3 methyl-4 dimethylaminezobene) to both normal and hypophysectomized rats. The experimental group was completely free of hepatoma after a period of 19 weeks. In the normal rats there was a 100% tumor incidence in half that length of time. The group conclude that some hormone or hormones from the pituitary are definitely involved in Azo dye liver carcinogenesis. Richardson (16) had another series in which hypophysectomy was carried out at seven weeks on rats which had already been receiving the Azo dye. This didn't check the tumor growth. Richardson felt that after changes start to occur, absence of the pituitary gland

will not reverse the process.

In an effort to determine what hormone was involved, these same investigators (17, 18, 19) divided the hypophysectomized rats into several groups. Each group of rats was then given a different pituitary extract. They found that growth hormone restored the carcinogenic activity of the Azo dye. ACTH partially restored it, while those receiving cortisone, DOCA, testosterone and pituitrin still did not develop tumors.

Moon, Simpson et. al. (20, 21) injected fifteen female rats intraperitoneally with pure pituitary growth hormone every day for 485 days. Ten rats (22) showed neoplastic cells displacing and invading the adrenal cortex. Lymphosarcomas were found in six. Five rats showed atypical hyperplasia of the ovaries (23) with two rats having solid tumors of the ovary. There were no neoplasms in control animals. The group is of the opinion that the growth hormone is an important factor in the occurence of neoplasms.

In 1953, Archer (24) made a complete review of the literature on case reports of Simmonds' Disease. There was not one case in which there developed carcinoma of the breast or ovaries. There were, however, several cases with other types of carcinoma. He concludes that

for this reason hypophysectomy may be beneficial to patients with carcinoma of the breast.

In recent years, surgical ablation of the pituitary has been performed on several different types of neoplastic disease. Scott (25) did surgical hypophysectomy on five cases of far advanced prostatic carcinoma. These patients had all relapsed following response to castration-estrogen therapy. Two had good response to the operation. Ray reports on four cases of carcinoma of the prostate and only one responded.

Ray (26) has carried out hypophysectomy in malignant melanoma, choriocarcinoma, hypernephroma, ovarian carcinoma, thyroid carcinoma and reticulum cell sarcoma. None had significant remissions and all were considered as failures. Luft and Olivecrona (27) report a temporary remission in an 18 year old girl with malignant chorioepithelioma.

A hypophysectomy was done by Knowlton (28) in metastatic adrenocortical carcinoma. The patient only lived for a month, with no evidence of regression. Shimkin et. al. (29) hypophysectomized a 32 year old man with malignant melanoma, who only survived nine weeks post-op.

The greatest majority of investigators have utilized the procedure in carcinoma of the breast.

The bigger series have been reported by Luft and Olivecrona (30, 27), Ray et. al. (26, 31) and Kennedy (32). Others having performed the operation in breast carcinoma are Startebecker (33), Rothenberg (34), LeBeau (35), Forrest (36) and Russell (37).

With the exception of breast carcinoma, hypophysectomy has been almost a complete failure in the treatment of neoplastic diseases. It is now the general concensus of opinion that the operation should be considered only in metastatic carcinoma of the breast.

Other diseases in which the effect of hypophysectomy is being studied includes the following: diabetes mellitus (27, 38, 39, 40), Cushing's disease (41, 42, 43), malignant hypertension (27), epilepsy (44) and progressive malignant exopthalmos (45).

METHODS

Complete destruction or removal of the hypophysis is difficult to obtain and many different methods have been attempted. In addition to choosing a method most likely to result in complete hypophysectomy, it is also desirable to use a procedure with minimal amount of trauma to the patient.

Kelly et. al. (46) attempted to destroy the hypophysis with massive doses of x-ray. This was attempted in three adult women, using a total of eight to ten thousand roentgen through multiple parts. There was no evidence of decreased pituitary function, which was substantiated later on necropsy studies by the finding of no histologic abnormalities in the hypophysis.

Rothenberg and his group in California (34) have been experimenting with the use of radioactive chromic phosphate. This substance has a half life of two weeks and gives off beta radiation only. It is injected into the hypophysis with a fine needle, with the pituitary receiving an estimated 2,000,000 to 5,000,000 beta roentgen equivalents. They have not as yet reported in the literature how successful they have been at completely destroying the gland in this manner.

Rasmussen (47) performed a series of experiments in monkeys, using radio active yttrium pellets to

inactivate the pituitary. These pellets emit beta rays and have a half life of sixty-two hours. Rasmussen then used this method in twenty-nine cases of metastatic carcinoma. In none of these patients was he able to obtain a complete hypophysectomy. He has abandoned the use of this method.

Leicher (48) describes the use of electrocoagulation in destroying the hypophysis. He used it in a few cases of acromegaly. This method, however, has not proved to be successful in inactivating hypophysial function.

Surgical hypophysectomy has been attempted by several approaches. Bronson Ray (26) first utilized a right temporal craniotomy to remove the pituitary. This method was used in sixteen patients, with only nine having a complete hypophysectomy. Besides there being two operative deaths, the morbidity rate was high. A transphenoidal approach was then tried in ten cases. The chief drawback to this procedure was the hazard of entering the venous plexus surrounding the sella while approaching along the anterior dural lining. Six of the patients died, with four of these deaths being due to meningitis.

A right frontal craniotomy is the most successful approach. This was used in fifty-three cases by Ray

and in thirty-seven cases by Luft and Olivecrona. After exposing the region by a right frontal flap, the right frontal lobe is retracted back and the right olfactory nerve is sectioned to give adequate exposure of the sella. The stalk is then coagulated and divided. The gland itself is curretted out, afterwards being treated with Zenker's solution to devitalize any remaining fragments of gland.

Radon seed implantation is the method employed by Dr. Kenneth Brown in the cases at U.N.H. presented in this paper. The radon seed consists of a small hollow gold pellet the size of a grain of rice, which is filled with radon gas. Radon emits alpha and gamma radiation, the gamma rays being the important one in destroying pituitary tissue. The half life of radon is less than four days.

A right fronto-temporal craniotomy is utilized, approaching the sella turcica along the right sphenoidal ridge. Using a curved lumbar puncture needle, the seed is deposited in the anterior portion of the sella turcica in the midline. One to three radon seeds are used, with a total dosage varying from 2.5 to 9 millicuries. There is too much danger of destroying surrounding brain tissue if larger dosages are used.

The radon seed implantation is much less difficult to perform than a complete hypophysectomy. One can use a smaller bone flap in placing a radon seed and the operation itself takes much less time than a hypophysectomy.

Forrest (36) has been perfecting a technique of implanting radon seeds, in which the sella turcica is approached intranasally. With the guidance of steriotyped radiography, a trocar is bored through the sphenoidal sinus and into the base of the sella turcica. The seeds are then placed through a canmula into the pituitary. This procedure is much less traumatic to the patient, since no opening is made into the intracranial cavity. If it prones successful, it can be used in patients who otherwise could not withstand a craniotomy.

CASE REPORTS

In addition to the five cases presented here, two other patients underwent radon seed implantation at U.N.H. which are not included in this analysis. The one patient was a 66 year old female on which the first operation of this type was performed. The seed was not properly placed, so that the radiation did not come in contact with the hypophysis. The other case was a 36 year old white male with cerebral metastasis from carcinoma of the colon. A frontal lobotomy was performed. At the same time two radon seeds totally 5 millicuries was placed in the hypophysis. This had no effect upon the course of his disease.

CASE REPORT #1

First Admission 1/15/31 to 3/1/51.

K. P., a 58 year old widowed housewife entered the U.N.H. for the first time complaining of a slowly growing mass in the left breast. The patient had a simple mastectomy performed on the left side seventeen years ago which the physician had told her was "chronic inflammation". She had been asymptomatic until one year ago, when she noted a lump in that breast, which slowly progressed in size. Physical examination revealed a 5x6x3 cm. hard, nontender mass at the lower medial pole of the surgical scar. The mass appeared to be fixed to the anterior chest wall. There were no palpable nodes in either axilla. On 1/10/51 the patient was taken to surgery and a biopsy of the lesion was performed. The frozen section report was "carcinoma". A left radical mastectomy was carried out. The final pathology report was undifferentiated carcinoma of the breast. She was dismissed on 3/1/51 in good condition, except for slight lymphedema of the left arm. No postoperative radiation therapy was given.

Interval History

The patient was seen in surgery clinic on 5/28/52, complaining of deep right subscapular pain of two months

duration. Examination revealed no evidence of recurrence of carcinoma in the left breast and lymph nodes, but a 3x4 cm. node in the right axilla was noted. She recieved no endocrine therapy.

Second Admission 6/10/52 to 6/21/52.

On admission, the patient had a mass over the left clavicle. It had been present two to three months and was slowly enlarging. On physical examination, a 1x2 cm. tender, firm mass was noted over and attached to the left clavicle. A firm 1x1 cm. tender, mobile mass was seen in the surgical scar. A 2x3x2 cm. mass was noted in the right axilla. A second mass, measuring 1x1 cm., lying inferior and medial to the above was also noted. Some lymphedema of the left arm was present.

It was decided to irradiate the metastatic lesions. The following dosages were given between 6/13/52 and 7/15/52: right axilla-1600r, right suprascapular region-2,200r, left suprascapular region-2,000r and left anterior thorax-2,000r.

Interval History

When seen in radiology on 9/26/52, no change in the metastatic lesions was evident. On 9/28/52 the patient felt well, but had pain in the mastectomy scar

and in the mass over the left clavicle. Physical examination revealed a 3x3x3 cm. mass in the right axilla which was tender to palpation. A small, slightly tender subcutaneous mass was present over the right clavicle. A third 2x3 cm. mass was noted over the left clavicle. Admission for biopsy of a lymph node was recommended.

Third Admission 10/15/52 to 10/27/52.

A biopsy of a node in the right axilla was done on 10/20/52. It was reported as adenocarcinoma of breast metastatic to axillary lymph node. A radiology consultation was obtained. No further x-ray therapy was recommended. It was felt by the surgery department that a trial of hormone therapy should be instituted. The patient was placed on 10 mg. of testosterone daily and dismissed.

Interval History

When seen on 11/24/52, the patient had been taking testosterone 10 mg/day for four weeks. She complained of pain of six months duration in the right shoulder and arm, in the region of the mass in the left supra-clavicular area and in the right breast. She noted the onset of headaches during the past month. On physical examination a 2x2 cm. mass in the mastectomy

was present. The mass in the left supraclavicular area measured 5x3 cm., whereas the mass in the right axilla was 2x3 cm. Testosterone was continued in the same dosage.

She was next seen in the surgery clinic on 12/8/52. She complained of pain in the right breast and axilla. The left supraclavicular mass and the mastectomy scar mass were painful also. The physical examination revealed the same masses as previously seen. In addition, a new mass in the right supraclavicular region measuring 2 cm. in diameter was also noted. The testosterone was discontinued and she was started on stilbesterol, 10 mgm/day for one week, then 20 mgm/day.

During the spring and summer of 1953, the patient continued to take 20 mgm. of stilbesterol/day and was seen several times in the surgical and radiologic clinics. Her metastatic lesions increased in size and she had periods of confusion and impaired memory. Her right arm became so difficult to control that she could no longer sew. Pain at the site of metastases was a prominent complaint. Her appetite was poor with a weight loss of 21 pounds. By the fall of 1953, the right breast was markedly enlarged, tense and had a

"pig skin" appearance. All visible metastatic lesions were progressing.

Fourth Admission 11/3/53 to 11/21/53.

On physical examination the status of the metastatic lesions was as follows: left clavicular mass, 3x5 cm., covered by red, thin skin which was ulcerated over the center of the lesion, tender to palpation; left mastectomy scar mass, 5x5 cm., stony hard; right breast, hard, tender, indurated 10x12 cm. mass in the right upper quadrant, the entire breast being pink in color; right axilla, 2x2.5 cm. ulcerating mass; and multiple subcutaneous nodules over the abdomen and one in the region of the labia majora were present.

Pre-operative laboratory data is presented in chart #1. B. P. 140/80.

On 11/10/53 a 2.31 millicurie radon seed was inserted into the hypophysis under direct vision utilizing a right fronto-temporal approach. A post-operative roentgenogram demonstrated the radon seed in the anterior portion of the pituitary fossa. Aside from headaches during the first week, the post operative course was uneventful with the patient being ambulatory on the second postoperative day.

At the end of the first postoperative week the right breast was no longer swollen or tender. She no longer complained of pain in the metastatic lesions, most of which has regressed about 50% in size. Her appetite was good and she was almost euphoric in her attitude. Visual fields remained full after surgery and no diabetes insipidus developed. She was dismissed 11/21/53 on no medication.

Fifth Admission 11/30/53 to 12/12/53

The patient was readmitted for laboratory studies (chart #1). She stated she had been feeling "just wonderful". She noted return of normal strength to her hands and arms, has had no pain postoperatively at the site of the metastatic lesions. She was able to do sewing now with her right hand, which she had been unable to do for the past year. On physical examination, the formerly described masses in the right breast, over the left clavicle and over the sternum had decreased in size to approximately one-third their preoperative measurements. The patient continued to feel good during her hospital stay.

Sixth Admission 1/4/54 to 1/23/54

The patient was again readmitted for laboratory studies (chart #1). She had felt well since her last dismissal. It was the opinion of the staff who had

seen the patient on previous admissions that the marked regression of the metastatic lesions remained evident. On 1/9/54, lesions in the area of the right axilla, in the mid-region of the mastectomy scar on the left anterior chest wall and one of the skin metastasis of the upper abdominal wall were biopsied. Comparison of these biopsies with previous ones showed no definite difference from the preoperative biopsies, except there appeared to be more fibrous tissue in the sections made after the radon seed implantation.

Interval Note

On 2/23/54, the first objective evidence of a recurrence of growth of metastatic lesions was noted. The left supraclavicular lesion was reddened and enlarging. The right breast was also larger and showed some redness laterally.

Seventh Admission 2/23/54 to 4/11/54.

She was readmitted to the hospital and a "metastatic" series of roentgenograms indicated that the pelvic metastasis had increased in size in comparison with a previous examination in December, 1953.

On 3/4/54, she had a left frontal craniotomy and three radon seeds totalling 7½ millicuries were inserted into the hypophysis. Her immediate post-operative

condition was good, except for severe headaches. The second operation did not cause any objective improvement in the size of the metastatic lesions, though again she received good palliation from recurrent pain.

On 3/25/54 the patient had a sudden "fainting" spell and went into a shocklike state. Her blood pressure ranged from 112/70 to 80/50. The pulse became weak but regular. She was given 300 mgm. cortisone orally and improved within an hours time.

She was discharged 4/11/54 on 25 mgm. of cortisone daily.

Interval History

Although the patient had a subjective feeling of well being, gained weight and did not complain of pain, most of her metastatic lesions increased in size during the summer of 1954. Her right breast continued to enlarge and it was obvious her cancer was progressing, although some of the skin metastasis were becoming smaller.

Eighth Admission 1/13/55 to 3/29/55.

She was re-admitted on 1/13/55 for oophorectomy and adrenalectomy. Following the operations, she became progressively worse and died on 3/28/55 without benefit from the above procedures.

CASE REPORT #2

First Admission 8/24/53 to 10/17/53

T. T., a 47 year old housewife entered U.N.H. complaining of a mass in the left breast of five weeks duration. She first noted a small, firm mass, but within a week the entire breast was enlarged, firm, reddened and hot to the touch. She also complained of pain in the right hip. The patient had been previously hospitalized at U.N.H. in 1950, at which time a lump was excised from her right breast. Pathology reported it to be intra- and peri-canilicular fibroadenoma; fibrocystic disease; and sclerosing adenosis. Earlier in 1950, the patient underwent both a right and left lumbar sympathectomy and greater splanchnicectomy for hypertension.

Physical examination revealed a markedly obese woman. There was A-V nicking with marked sclerosis of the retinal vessels. The left breast was enlarged, firm, warm to the touch, with an "orange peel" appearance to the skin. The outer three-fourths of the right breast was nodular, firm and fibrous feeling. A grade II aortic systolic murmur transmitted to the neck could be heard, in addition to a grade I apical blowing systolic murmur. Blood pressure was 234/140.

Laboratory values were all in normal range. X-ray of the chest revealed the transverse cardiac diameter to be at the upper limits of normal. An EKG showed left ventricular strain and hypertrophy. An x-ray of the pelvis reported possible metastatic lesions of the pelvis and right femoral neck.

Both breasts were biopsied and reported as bilateral adenocarcinoma. The patient was started on deep x-ray therapy, receiving the following dosage: anterior tangential of left breast - 2,100 r, left breast - 2,090 r, left supraclavicular area - 2,280 r, left axillary region - 1,323 r.

Therapy was then begun on the right breast and she was discharged on 10/17/53 to return in a few days for further therapy.

Second Admission 10/21/53 to 12/24/53

After receiving the same dosage of x-ray therapy to the right breast as on the left, she also received a sterilizing radiation dosage to both ovaries. Because of intermenstrual bleeding, a D and C and wedge biopsy of the cervix was done on 11/11/53. This was reported as metastatic carcinoma of the breast to endometrium and cervix. X-rays taken on 11/24/53 revealed multiple metastatic lesions of skull, ribs and pelvic bones.

The patient was seen by the Neurosurgical department and it was decided to do a radon seed implant. At the time of operation, the status of her breasts were as follows: left breast, 8x10x5 cm. hard, firm mass; right breast, 7x7x6 cm. mass and a 4x4 cm. nodule which extended into the right axilla; right axilla, 2.5x3 cm. hard nodule; left axilla, no palpable nodes. On 12/1/53 a radon seed of 3 millicuries was inserted in the hypophysis, utilizing a right temporal approach. X-ray showed the seed to be lying in the floor of the pituitary fossa, slightly to the left of the midline. The patient's immediate postoperative condition was satisfactory.

By the third post-op day, the patient was ambulating, eating well and had no complaints. The pain in her right hip had disappeared. She felt that her breasts were less firm. Her blood pressure remained elevated. X-rays of the metastatic lesions in the skull and chest showed no significant change.

Postoperative tests were completed (chart #2), and the patient was discharged on 12/24/53.

Third Admission 1/25/54 to 2/7/54

The patient was readmitted for laboratory studies (chart #2). She had been comfortable without any pain.

Her appetite was good and there was a three pound weight gain since last admission. No polyuria or bluring of vision had developed. Objectively, there was no change in the size of the breast lesions.

X-ray films showed slight progression in the size of all previously reported bony metastasis, in addition to new osteolytic lesions in the lumbar spine. A gynecologic consultation reported no change in the status of the uterus and cervix.

Fourth Admission 3/17/54 to 4/11/54.

The patient re-enters U.N.H. for the fourth time complaining of dull, non radiating pain in the left hip. Physical examination revealed that the metastatic breast lesions were not regressing in size. In addition, several large indurated nodes could be felt in the left axilla. Also a new mass measuring 3x5 cm. was noted at the base of the neck on the right. Her blood pressure remained elevated at 220/110.

It was evident that the patient's metastatic involvement was progressing. On 3/26/54 three radon seeds of 2.5 millicuries each were implanted in the pituitary through the previous craniotomy flap without difficulty. Her immediate postoperative condition was good, except for the presence of severe headaches requiring frequent sedation.

The patient had very little relief of her hip pain post-op. There was no improvement of metastatic lesions on x-ray. Her condition was essentially unimproved at time of discharge on 4/11/54.

Fifth Admission 4/19/54 to 5/9/54.

The patient re-enters with a history of feeling very tired and anorexic. She recently had the onset of polyuria and polydipsia, getting up four to six times a night to drink water. The urine had a specific gravity which ranged from 1.001 to 1.004 and the daily urinary output was between four and six liters. She was started on intramuscular pitressin.

Visual field examination showed some diminution of the peripheral fields. There was no evidence of muscle paresis.

After the regulation of urinary output, the patient was dismissed on the following medication: 2/3 gr. powdered pituitary extract by nasal insufflation and 12.5 mgm. cortisone twice daily.

Sixth Admission 5/24/54 to 6/8/54.

The patient was re-admitted to undergo deep x-ray therapy to the pelvic region for relief of bone pain. She received a total of 2,214 r to the pelvic area from PA and AP ports. On 6/1/54 she was started on intra-

muscular testosterone (25 mgm. three times weekly). On this regime, she developed some nausea, vomiting and mental depression, which subsequently disappeared.

She was dismissed 6/8/54 on powdered pituitary extract, oral testosterone and dilaudid for pain.

Interval History

During the summer months of 1954, the patients hip and shoulder pain gradually improved. She was able to take care of her housework. However, during the first week of August she became troubled with diplopia.

Seventh Admission 8/23/54 to 10/13/54.

The patient was re-admitted for the seventh time complaining of severe constant diplopia. Physical examination revealed bilateral papilledema. There was also a bulging, soft protuberance through burr hole in right frontal region. Several new enlarged lymph nodes were present. Breast lesions remained unchanged. B. P. still elevated at 200/110.

Visual field tests showed bilateral visual field loss to about ten degrees concentrically. Metastatic x-ray series showed progression of osteolytic lesions.

It was necessary to instill an indwelling catheter because of incontinence. The patient became quite

lethargic and apathetic and it became necessary to supplement her oral intake with IV fluids. She was considered a terminal care problem and discharged to a rest home.

Interval Note

Over the next few months, she had progressive loss of vision, finally having light perception only. It was necessary to give her frequent narcotics for pain.

Eighth Admission 1/21/55 to 2/14/55.

The patient was brought to the admitting room after the sudden onset of a convulsive episode during the night. She responded to painful stimuli only and exibited spasmodic focal seizures which appeared to be more marked on the right side.

With heavy sedation, her convulsive seizures stopped a week after admission. She was dismissed to a nursing home. Her condition continued to become worse and she died a few months later in a hospital in Weeping Water, Nebraska.

CASE REPORT #3

M. B., a 37 year old white female, first entered U.N.H. on 1/26/54 complaining of marked swelling, pain and inflammation of her right breast of a years duration.

The patient first noted a lump in the lower outer quadrant of the right breast. This subsided somewhat until 2½ months ago when she suddenly became feverish. The right breast became enlarged and inflammed, with agonizing pain in the right breast, shoulder and arm. A few days later the right arm and hand became tremendously swollen. A month before admission, her neck became swollen and she felt large nodules on each side.

Physical examination revealed tremendous enlargement, marked tenderness, induration and fixation of cervical and supraclavicular nodes bilaterally. There was noted congestion of superficial venous system over the right thorax anteriorly. The right breast was enlarged, exquisitely tender and erythematous. There was grade IV pitting edema of right arm and shoulder. Large nodes were palpable in the right axilla. The liver could be felt below the RCM.

An x-ray of the chest showed increase in size and density of the soft tissue overlying the right thorax compatible with the presence of an inflammatory type of breast carcinoma. Elevation of the right diaphragm indicated presence of an enlarged liver. A hazy clouding of right paratracheal area was thought to be an enlarged right paratracheal node. Metastatic series

with films of skull, ribs, lumbar spine and pelvis failed to reveal any evidence of bony metastasis. On 1/29/54 a cervical node was biopsied and reported as a highly undifferentiated neoplasm invading and replacing lymph nodes, probably carcinoma.

The surgical staff was of the opinion that there were no therapeutic measures which could be offered to the patient other than terminal care and relief of pain. It was decided to do a radon seed implantation to see if it would have any affect on the growth of the tumor. On 2/2/54, the patient was taken to surgery and two radon seeds were inserted in the pituitary with a total dosage of 5 mc. The patient left the operating room in good condition. X-ray reported the radon seeds within the sella turcica.

Immediately post-operative, the patient felt much better subjectively, complaining only that at times her eyes "grew dim". Objectively, on the third post-op day it seemed that the redness was leaving the periphery of the breast, but it appeared the same as usual a few days later. The neck and skin metastasis increased in size. The patient became rapidly and progressively worse. She died on 3/8/54 with no evident benefit from the procedure.

CASE REPORT #4

First Admission 3/7/54 to 3/31/54.

E. B., a 58 year old white female first entered U.N.H. on 3/7/54 complaining of burning in the pit of her stomach, shortness of breath and pain in her right shoulder. In 1947 the patient had a radical mastectomy performed on the left side. Sections of the tumor mass revealed it to be a well differentiated adenocarcinoma. The patient was asymptomatic following surgery until one year ago. At this time she developed a burning mid-epigastric pain. She was placed on a bland diet and antiacids at the U.N.H. dispensary. However, her symptoms were not relieved and in addition, she began having right shoulder pain and shortness of breath. On 12/9/53, x-ray reported osteolytic changes in the right proximal shaft of the humerus, indicative of metastatic carcinoma from breast. She was started on 110 r of deep x-ray to the upper one-third of the right humerus daily, receiving a total dosage of 2090 r. She was also started on testosterone, 150 mgm. intramuscularly every week. On 12/21/53 beginning demineralization of the lumbar spine was noted and she received a total dosage of 1710 r to this area. Her condition

remained unimproved, so it was decided to hospitalize her.

Physical examination revealed her to be a well developed, rather poorly nourished woman. A 3x4 firm, tender nodule was felt along the left posterior cervical chain. There were no masses palpable in the breast. Generalized tenderness was noted in the L.U.Q. and the liver was palpable three fingers below RCM. Abduction was limited in the right shoulder.

X-rays taken on admission reported same findings as before, with the addition of bony metastasis to pelvis. The patients laboratory data is presented in chart #3.

On 3/18/54 she was taken to surgery and 3 radon seeds, with a total dosage of 9 millicuries, was placed in the pituitary gland without difficulty. Her immediate post-op condition was good, except for a few days of nausea and vomiting. She was discharged on 3/31/54, after completion of laboratory tests.

Second Admission 4/10/54 to 5/9/54.

The patient was re-admitted complaining of nausea and vomiting of two days duration. The pain in her right shoulder and pelvic area had disappeared a couple weeks after the radon seed implant. On physical exam-

ination, she appeared to be slightly dehydrated and intravenous fluids were started. On 4/11/54 50 mgm. of cortisone intramuscular q.i.d. was instituted, which stopped the vomiting. This dosage was gradually decreased. A few days later, there was onset of diabetes insipidus, with the output of large volumes of urine of low specific gravity. She was placed on I.V. pitressin.

Visual field studies on 4/27/54 showed slight decrease in fields bilaterally. X-ray reported no change in the metastic bone lesions. After getting her diabetes insipidus under control, she was dismissed on 5/9/54 on cortisone (2.5 mgm. b.i.d.) and nasal posterior pituitary capsules.

Third Admission 5/24/54 to 6/6/54.

The patient re-enters because of severe back pain in the thoracic area which has increased in severity. The hip and shoulder pain has not recurred. She was started on 123 r of deep x-ray to the mid-dorsal spine daily, receiving a total dosage of 1189 r. She was dismissed somewhat improved 6/6/54 and was to continue the same medication.

Interval History

During the summer, the patient improved subjectively,

having no pain. Her appetite continued to improve and she gained weight. However, during the first week of July she noted blurring of her vision and this gradualy became worse. An eye examination on 7/19/54 revealed loss of vision in the left upper temporal field of the left eye.

Fourth Admission 9/2/54 to 9/22/54.

The patient was re-admitted because of marked blurring of vision. Otherwise, she stated that she felt better than she had for a whole year. She had no back pain. An eye consultation reported left temporal hemianopsia, with light perception only in the right eye. Left and right carotid arteriograms were done and no abnormalities were noted. X-rays on 9/7/54 showed multiple osteoplastic sites within the pelvis suggesting metastasis. She was discharged on 9/22/54 in good condition, except for vision.

Fifth Admission 9/26/54 to 10/27/54.

The patient was brought to the emergency room by the rescue squad, after being found on the bed unable to move. She was conscious, but aphasic. Soon after admission, she had a left sided clonic convulsion, becoming quite cyanotic. Physical examination revealed her to be aphasic, answering questions

by nodding her head yes or no. Eye movements were jerky. The pupils were dilated and reacted to light sluggishly. Deep tendon reflexes were absent. She was unable to move her left arm or leg. There was a positive Babinski on the right side.

She was placed on bed rest and given parenteral fluids, cortisone and sedation. Neosynephrine was used occasionally for hypotension and she received two blood transfusions. Her condition improved rapidly and there were no more convulsive episodes. She was dismissed 10/27/54 on nasal pitressin and 25 mgm. of cortisone daily.

Sixth Admission 2/10/55 to 3/19/55.

The patient was re-admitted for the sixth time complaining of back pain in the thoracic area, which had become so severe that she had been bedfast for a week. This pain was aggravated by movement. X-rays of the thoracic spine showed collapse of T-5 and 6 due to marked progression of osteolytic activity. She was started on deep x-ray therapy to the involved area, receiving a total of 693 r. This led to moderate improvement of back pain. However, the patients generalized condition did not improve and she was discharged to a nursing home for terminal care. She

died five months later on 8/19/55 from gradual progression of her disease.

CASE REPORT #5

First Admission 4/25/51 to 7/6/51.

A. L., a 70 year old white woman enters U.N.H. complaining of intermittent pain in the upper left arm of two years duration and painless swelling of the same arm for the past two months. Physical examination revealed a 1½ x 1½ cm. indurated mass in the left anterior axillary region. A small, hard nodule was also noted inferior to the left clavicle. There was a 2 + pitting edema of the left arm. No masses or nodules were palpable in either breast.

On 5/3/51 the left subclavicular mass was biopsied and reported as metastatic adenocarcinoma, probably from breast. This was followed by a radical mastectomy on the left side. Grossly, a firm fibrous area was located in the breast specimen. The microscopic report of this tissue was adenocarcinoma of the breast, well differentiated, with axillary lymph node metastasis. The patient was then given irradiation therapy to the axillary region, receiving a total dosage of 2,040 r. She was dismissed 7/6/51 in good condition.

Second Admission 4/20/53 to 5/10/53.

The patient re-enters U.N.H. complaining of pain in the right hip of eleven weeks duration. She also had noted some "lumps" in her left axilla. Physical examination revealed several il-defined, hard masses measuring approximately 2x2 cm. at the lateral border of the latissimus dorsi muscle in the left posterior axillary line. Lumbosacral x-rays showed compression collapse of the first lumbar vertebra, appearing to be a metastatic lesion.

She was started on deep x-ray therapy, receiving 990 r to the left medial upper arm and 1300 r to the first lumbar vertebra. Three radium needles of 2 mgm. each were placed in the left posterior axillary region for a total dosage of 720 mgm. hours. She was dismissed on 5/10/53 to be followed in tumor clinic.

Third Admission 4/21/54 to 6/13/54.

Patient re-enters the hospital complaining of, (1) severe pain in the lower back radiating to both hips and (2) painful lumps in the neck, left axilla and in the previous mastectomy scar. Physical examination revealed her to be a senile, fairly well nourished woman who appeared to be chronically ill. There was marked fullness of the left supraclavicular

fossa due to edema. A 2x2 cm. hard, fixed nodule was palpated at the base of the neck on the left side. The left anterior axillary region was firm, indurated and nodular. Multiple hard, fixed nodules were located along the left mastectomy scar. Some of these nodules had ulcerated centers. The left arm was enlarged with some pitting edema. The spine showed slight left dorsal scoliosis.

An x-ray of the chest on 4/28/54 showed coarsened markings in the right mid lung field and also in the left lower lung, which was interpreted to be lymphangitic spread of carcinoma of breast to both lungs. Lumbar films revealed a compression fracture with metastatic destruction of L-1. A biopsy of one of the nodules in the mastectomy scar was reported as metastatic adenocarcinoma.

On 5/14/54 three radon seeds of three millicuries each were inserted in the pituitary, utilizing a right frontal craniotomy. Her immediate post-op condition was good, with the patient responding and recognizing people by the same afternoon. On the second post-op day, the patient felt the pain in her left shoulder and back was much improved. By the end of a week, she was ambulatory and felt good except for slight back pain.

There was noticeable decrease in the size of the metastasis over the left lateral chest wall and upper arm.

After completion of laboratory tests (chart #4), she was dismissed from the hospital 6/13/54 on 12½ mgm. of cortisone twice daily. She was to return to the x-ray department on an out-patient basis to receive x-ray therapy to her back. She received a total dosage of 1107 r to the first lumbar vertebra.

Fourth Admission 6/21/54 to 6/28/54.

The patient was readmitted to be fitted with a Taylor spine brace for relief of back pain. It was noted that several subcutaneous nodules at the left base of the neck and over the sternum had diminished in size since the last admission. X-ray reported some clearing of the lung fields since previous examination, with no new areas of metastasis.

The patient was placed on testosterone, 10 mgm. three times a day, for possible relief of back pain. She was also to continue on 12½ mgm. of cortisone twice daily.

Interval History

The patient was seen in neurosurgical clinic on 7/12/54. Her back pain had decreased in severity. The

subcutaneous masses were still regressing in size, with no new evidence of metastasis.

The patient didn't return to the clinic until 8/22/55. She had been feeling good and had done her own housework for the past year. Her back pain had disappeared and she had discontinued wearing the brace. She also reported some weight gain. Physical examination revealed that three nodules in the left axilla had disappeared. No new skin nodules had appeared. Her vision was unchanged. Her cortison dosage was decreased from 12½ mgm. b.i.d. to 12½ mgm. once a day. She was to continue the same dosage of testosterone.

The patient continued to feel well until December, at which time she had the onset of pain and swelling in the left arm and shoulder. She also started having pain in both legs.

Fifth Admission 3/21/56

On 3/21/56 she re-entered the hospital. Physical examination revealed many subcutaneous nodules to be recurring. There was generalized edema of the left arm and also slight swelling of both legs. X-ray examination revealed definite increase in the size and number of metastatic lesions in comparison with films taken previously. There was almost complete

destruction of the vertebral body of L-2. At the time of preparing this paper, no other data is available. She is still in the hospital and is in the process of having a complete investigation of her clinical status.

Test	Pre-Op	Post-Operative 1-4 wks.	Post-Operative 4-8 wks.	2 weeks after second operation
17 keto steroids	12.6 mg./24 hr.	19.7 mg/24 hr.	16.5 mg./24 hr.	4.1 mg./24 hr.
BMR	⁄8%	-14%	⁄17%	
I^{131} uptake				
4 hr.	16.5%		11%	
24 hr.	26.5%		14%	
48 hr.	28.0%		16%	
Glucose Tolerance				
Fasting	93 mg.%	88 mg.%	86 mg.%	
½ hr.	182 mg.%	140 mg.%	180 mg.%	
1 hr.	220 mg.%	143 mg.%	170 mg.%	
1½ hr.	189 mg.%	156 mg.%	138 mg.%	
2 hr.	192 mg.%	125 mg.%	60 mg.%	
3 hr.	99 mg.%	115 mg.%	65 mg.%	
4 hr.	55 mg.%	80 mg.%	55 mg.%	
Insulin Tolerance				
Fasting		75 mg.%		80 mg.%
½ hr.		70 mg.%		75 mg.%
1 hr.		68 mg.%		70 mg.%
1½ hr.		60 mg.%		65 mg.%
2 hr.		65 mg.%		65 mg.%
3 hr.		75 mg.%		65 mg.%
4 hr.		68 mg.%		70 mg.%
Thorne				
Fasting	190/cu.mm.	500/cu.mm.		
4 hr. after ACTH	0/cu.mm.	175/cu.mm.		
Epinephrine				
Fasting		275/cu.mm.	388/cu.mm.	
After epinephrine		100/cu.mm.	162/cu.mm.	

Chart #1
Laboratory Data-K. P.

Test	Pre-Op	Post-Operative 1-4 wks.	Post-Operative 4-8 wks.	2 weeks after second operation
Hgb.	13.2	12.5	12.5	12.8
WBC	8,000	5,200		6,500
NPN	30.5 mg.%	33 mg.%		
TSP	6.8%	7.3%	7.15%	6.9%
Serum Albumin	3.3%	4.0%	4.12%	3.4%
Serum Globulin	3.5%	3.3%	3.03%	3.5%
CO_2	24.6 mEq/L	22.1 mEq/L	23.7 mEq/L	23.3 mEq/L
Serum Na	138 mEq/L	140 mEq/L	145 mEq/L	133 mEq/L
Serum Cl	99 mEq/L	107 mEq/L	112 mEq/L	103 mEq/L
Serum K	5 mEq/L	5.2 mEq/L	5 mEq/L	5 mEq/L
Serum Ca		9.4 mg.%	11.7 mg.%	9.4 mg.%
Inorganic Phosphate		3.46 mg.%	2.88 mg.%	
Cholesterol		375 mg.%	350 mg.%	317 mg.%
Cholesterol Esters		80%	80%	78%

Chart #1 continued
Laboratory Data-K. P.

Test	Pre-Op	Post-Operative 1-4 wks.	Post-Operative 4-8 wks.	2 weeks after second operation
17 keto steroids	3.7 mg./24 hr.	2.4 mg./24 hr.	3.7 mg./24 hr.	5.8 mg./24 hr.
BMR	⁄4%	⁄8%	⁄12%	
I^{131} uptake				
4 hr.	11%		9%	12%
24 hr.	14%		18.5%	13.5%
48 hr.	14.5%		23%	20.5%
Glucose Tolerance				
Fasting	100 mg.%	105 mg.%	95 mg.%	
½ hr.	118 mg.%	152 mg.%	50 mg.%	
1 hr.	121 mg.%	152 mg.%	85 mg.%	
1½ hr.	116 mg.%	120 mg.%	85 mg.%	
2 hr.	130 mg.%	118 mg.%	85 mg.%	
4 hr.	104 mg.%	87 mg.%	85 mg.%	
Insulin Tolerance				
Fasting	56 mg.%			95 mg.%
½ hr.	33 mg.%			78 mg.%
1 hr.	27 mg.%			88 mg.%
1½ hr.	Insulin			97 mg.%
2 hr.	reaction			92 mg.%
3 hr.				85 mg.%
4 hr.				68 mg.%
Thorne				
Fasting	175/cu.mm.	125/cu.mm.	200/cu.mm.	
4 hr. after ACTH	150/cu.mm.	88/cu.mm.	88/cu.mm.	
Epinephrine				
Fasting		138/cu.mm.		
After epinephrine		60/cu.mm.		

Chart #2
Laboratory Data-T. T.

Test	Pre-Op	Post-Operative 1-4 wks.	Post-Operative 4-8 wks.	2 weeks after second operation
Hgb.	11.2	9.8	11.9	12.5
WBC	4,100	4,000	5,300	5,800
NPN	43 mg.%	41 mg.%	40 mg.%	40 mg.%
TSP	6.35%	7.65%	8.15%	6.8%
Serum Albumin	3.96%	4.72%	4.2%	3.8%
Serum Globulin	2.39%	2.93%	2.5%	3.0%
CO_2	27.2 mEq/L	25.5 mEq/L		29 mEq/L
Serum Na	150 mEq/L	165 mEq/L	142 mEq/L	150 mEq/L
Serum Cl	111 mEq/L	103 mEq/L	104 mEq/L	110 mEq/L
Serum K	5.2 mEq/L	4.7 mEq/L	4.6 mEq/L	4.7 mEq/L
Serum Ca	10.5 mg.%	10.5 mg.%	10 mg.%	10.4 mg.%
Inorganic Phosphate	4.08 mg.%	4.2 mg.%	5.28 mg.%	
Cholesterol	229 mg.%	240 mg.%	258 mg.%	284 mg.%
Cholesterol Esters		80%	66%	82%

Chart #2 continued
Laboratory Data-T. T.

Test	Pre-Op	2 weeks Post-Op
17 keto steroids	1.3 mgm./24 hr.	1.13 mgm./24 hr.
Glucose Tolerance		
Fasting	85	
½ hr.	143	
1 hr.	189	
1½ hr.	157	
2 hr.	160	
3 hr.	149	
4 hr.	120	
Thorne		
Fasting	0/cu.mm.	
4 hrs. after ACTH	0/cu.mm.	
Hgb.	14	13.6
WBC	8,400	13,500
NPN	33 mg.%	42.6 mg.%
TSP	6.0%	5.65%
Serum Albumin	3.02%	2.96%
Serum Globulin	2.98%	2.69%
CO_2	27.9 mEq/L	22 mEq/L
Serum Na	140 mEq/L	131 mEq/L
Serum Cl	110.8 mEq/L	102 mEq/L
Serum K	5.2 mEq/L	5.2 mEq/L
Serum Ca		8.5 mEq/L
Cholesterol	93 mg.%	75 mg.%
Creatinine	.7 mg.%	1 mg.%

Chart #3
Laboratory Data-M. B.

Test	Pre-Op	Post-Operative 1-2 wks.	3-4 wks.	6 months
17 keto steroids	9.3 mg./24 hr.	4.9 mg./24 hr.	8.8 mg./24 hr.	
BMR	⁄7%	-35%		-37%
	⁄11%	-38%		
I^{131} uptake 4 hr.	12%			5%
24 hr.	15%			7%
48 hr.	15%			6%
Glucose Tolerance				
Fasting	90 mg.%			65 mg.%
½ hr.	135 mg.%			95 mg.%
1 hr.	158 mg.%			103 mg.%
1½ hr.	60 mg.%			100 mg.%
2 hr.	60 mg.%			85 mg.%
3 hr.	38 mg.%			80 mg.%
4 hr.	60 mg.%			80 mg.%
Insulin Tolerance				
Fasting	71 mg.%	89 mg.%		97 mg.%
½ hr.	89 mg.%	65 mg.%		41 mg.%
1 hr.	81 mg.%	77 mg.%		
1½ hr.	81 mg.%	77 mg.%		71 mg.%
2 hr.	77 mg.%	89 mg.%		95 mg.%
3 hr.	87 mg.%	84 mg.%		80 mg.%
4 hr.	102 mg.%	102 mg.%		88 mg.%
Thorne				
Fasting				12.5/cu.mm.
4 hr. after ACTH				12.5/cu.mm.

Chart #4
Laboratory Data-E. B.

Test	Pre-Op	Post-Operative 1-2 wks.	3-4 wks.	6 months
Hgb.	14.4	13.6	11.9	11.9
WBC	5,500	9,600	4,500	4,800
NPN	41 mg.%	35 mg.%	31 mg.%	34.6 mg.%
TSP	8%	7%		8.55%
Serum Albumin	4.2%	3.36%		4.22%
Serum Globulin	3.8%	3.64%		4.33%
CO_2	31.9 mEq/L		27.6 mEq/L	28.0 mEq/L
Serum Na	147 mEq/L	130 mEq/L	140 mEq/L	146 mEq/L
Serum Cl	111 mEq/L	103 mEq/L	111 mEq/L	107 mEq/L
Serum K	5.1 mEq/L	4.4 mEq/L	4.6 mEq/L	4.4 mEq/L
Serum Ca	9.4 mgs.%	9.5 mg.%		12 mg.%
Inorganic Phosphate	3.84 mg.%	2.76 mg.%		2.88 mg.%
Cholesterol	217 mg.%	192 mg.%		267 mg.%
Cholesterol Esters	79%	79%		75%

Chart #4 continued
Laboratory Data-E. B.

Test	Pre-Op	2 weeks Post-Op
17 keto steroids	8.95 mg./24 hr.	6.2 mg./24 hr.
Insulin Tolerance		
Fasting	88 mg.%	90 mg.%
½ hr.	68 mg.%	40 mg.%
1 hr.	83 mg.%	75 mg.%
1½ hr.	85 mg.%	85 mg.%
2 hr.	87 mg.%	90 mg.%
3 hr.	87 mg.%	80 mg.%
4 hr.	87 mg.%	80 mg.%
Thorne		
Fasting	238/cu.mm.	1088/cu.mm.
4 hr. after ACTH	75/cu.mm.	388/cu.mm.
Hgb.	13.2	11.5
WBC	7,600	10,700
NPN	42 mg.%	33 mg.%
TSP	6.9%	5.9%
Serum Albumin	4.03%	3.1%
Serum Globulin	2.87%	2.8%
CO_2	25.9 mEq/L	23.2 mEq/L
Serum Na	130 mEq/L	151 mEq/L
Serum Cl	100 mEq/L	113 mEq/L
Serum K	3.9 mEq/L	5.5 mEq/L
Serum Ca	9.5 mg.%	9.3 mg.%
Inorganic Phosphate	3.8 mg.%	3.36 mg.%
Cholesterol	267 mg.%	267 mg.%
Cholesterol Esters	73%	78%

Chart #5
Laboratory Data-A.L.

DISCUSSION

Surgical Hypophysectomy

The total number of patients with mammary carcinoma to be evaluated are 116. Ray (49) has reported sixty-seven cases through March 1955. Luft and Olivecronas series (30) include thirty-seven cases up to June, 1954. Kennedy (32) has a smaller series of twelve patients reported to April, 1955. Others have been done, but are not as yet reported in the literature.

The present day concept (50) of treatment of carcinoma of the breast is to remove the diseased breast and regional nodes in a radical manner and follow with x-ray therapy. If the woman is premenopausal and has a recurrence of the cancer, oophorectomy is accomplished. This is followed with the use of androgens, estrogens and cortisone in varying sequence in an attempt to bring about further remission. After this fails, either an adrenalectomy or hypophysectomy is performed. Therefore, practically all patients selected for Hypophysectomy have far advanced lesions with multiple metastasis. They are all considered inoperable in relation to successful removal of the neoplastic tissue.

Ray (49) found that in women who had a previous remission with oophorectomy, a second remission was

affected in 100% of the cases. In ten patients who had previously responded to both oophorectomy and adrenalectomy, five had further remission from hypophysectomy. Therefore, hypophysectomy is indicated in those patients who have responded to either oophorectomy or adrenalectomy, especially in the former. Ray also reports that if a patient fails to respond to oophorectomy, there will likewise be no remission from hypophysectomy.

The failure of a breast lesion to respond to estrogen or androgen therapy does not appear to be a contraindication to hypophysectomy. Several of these have gone ahead and shown improvement following surgery, after receiving no benefit from hormonal therapy.

The younger patients seem to respond better than the older. Ray (49) feels that this is because the breast lesions in the younger group are more apt to be estrogen stimulated tumors. Most investigators now feel that women over sixty years of age should not be subjected to the procedure.

The histologic type of the tumor apparently has no bearing on the percentage of successful remissions. Regressions have been seen in the highly anaplastic invasive type, as well as in the well differentiated

ones. Olivecrona (30) noted that all of his cases of scirrous cancer had remission. However, this type was only present in four patients, which is not enough material to draw any conclusions from.

Ray (49) and Olivecrona (20) both report that the presence of brain or liver metastasis is a contraindication to the procedure. There has been no remission reported with metastasis to these two sites. In Olivecrona's series seven cases had brain or liver metastasis and they all died within a four month period following surgery.

The mortality and morbidity rate from the operative procedure itself is low, considering the general status of the patients coming to surgery. Eight of Rays (49) cases died within thirty days of the procedure. Most of these succumbed to their disease rather than operative complications. Ray had the complication of subcortical hematoma in two cases. One of Olivecronas (3) patients succumbed to a pulmonary embolism. Kennedy (32) reported three postoperative deaths due to pulmonary embolism, circulatory collapse and bacterial meningitis respectively. Visual disturbance as a complication was very uncommon.

The mortality rate was much higher in some of Rays and Olivecronas earlier cases which were not included

in the series now being evaluated. This was before the surgical technique of the operation was carefully worked out.

Other investigators also report that mortality and morbity figures improve after a group becomes organized into an efficient team in carrying out the procedure.

A patient was not considered to have a significant remission by Ray (49) unless there was some evidence of objective response to the hypophysectomy. This was determined by the presence of regression or cessation of tumor growth for a period extending more than two months following surgery. As soon as there was evidence of progression of old lesions or the appearance of new ones, the remission was considered to have ended. Luft and Olivecrona (30) evaluated the patients by almost the same criteria, considered those which died within three months as complete failures.

Of Rays sixty-seven cases, thirty three were considered to have objective remissions. Eight of these patients show no progression up to the present time. Olivecrona reported 15 remissions, from his series and Kennedy reports only four. The duration of the remissions ranges from three to twenty-eight months, with an

average of seven months. This cannot be evaluated fully as of yet, since most of the work has been too recent to determine the average duration of remission. Both Ray and Olivecrona expect the average to be a two year remission. The general condition of some of the patients was good enough that they could return to their ordinary activity. Remission is most evident in local skin metastasis; however, some cases showed improvement in lung and pleural metastasis, which was evident on x-ray findings. Bone metastasis occasionally will respond. The response of bone metastasis is difficult to evaluate, since there may be alleviation of pain from skeletal lesions in the absence of positive x-ray findings.

In a patient who had previously underwent oophorectomy and adrenalectomy with improvement, Ray (51) performed a hypophysectomy and gained a further remission. There was evidence of recalcification of osteolytic metastasis on x-ray. He then administered beef pituitary somatotropin (100 mgm. daily I.M.) to this patient. This resulted in a steady rise in urinary calcium excretion from 165 mgm. to 408 mgm/day, indicating restimulation of osteolytic activity. There was also a concomitant rise in urinary phosphorus, fecal

calcium and fecal phosphorus excretion. As soon as the hormone was discontinued, the calcium and phosphorus levels returned to normal.

The best results were obtained in the subjective relief of pain. Often there was marked symptomatic improvement, even in the absence of objective response. Many times excruciating skeletal pain which was present preoperatively would disappear altogether post-op. Olivecrona (30) reported on twenty-four patients who had pain before operation. Eighteen of these had complete disappearance or significant decrease in pain following hypophysectomy.

Hypophysectomy leads to the removal of various hormonal secretions from the circulation. This in turn causes several physiologic changes to occur. Most of these changes take place in the target organs and in the functions of metabolism controlled by these end organs.

After hypophysectomy, the patient will gradually develop clinical myxedema (52). The onset is insidious, with the skin becoming dry and later thick and scaly. They finally stop sweating, become mentally sluggish and gain weight. The average length of time for clinical hypothyroidism to become evident without

replacement therapy is eight weeks. These changes are made evident by a decrease in the radioactive iodine uptake to myxedematous levels. Before surgery the mean value in Rays cases (52) was 28.3%, which was lowered to 4.6% by four weeks following surgery. Concomitantly, the serum PBI level fell from a mean level of 5.8 microgram/100 cc. to 1.2. Ray noted a slight increase in serum cholesterol, but not enough to be significant.

To prevent hypothyroidism, patients were given 1.5 to 2 gms. of dessicated thyroid daily. Ray (49) used the radioactive iodine uptake value as a test for the completness of hypophysectomy. If below 15%, he considered it to be a complete hypophysectomy.

The patients will show evidence of adrenal insufficiency by the second week if replacement therapy is withheld. This can be shown by the determination of urinary keto steroid values, which Fraser (53) used as a diagnostic tool in Simmonds' disease. Luft and Olivecrona (54) found that the 17 keto steroids and corticoids reached a low level by as soon as the ninth post-op day. They remained at or near zero as long as substitution therapy was withheld.

Another test for adrenal insufficiency is the adrenaline test. In patients with complete hypophysectomy, Luft (30) reported there was no eosinopenic response when .3 mgm. of adrenaline was given subcutaneously, from the second post-op week on. In an autopsy report of a hypophysectomized case, Elden (44) found the adrenal glands to be markedly atrophied.

After hypophysectomy the patients practically all demonstrate insulin hypersensitivity. Luft (54) had a few patients who developed sudden hypoglycemic convulsions. These patients usually responded to intravenous glucose therapy. The insulin hypersensitivity can be diminished by giving cortisone. Sheehan (55) utilized the insulin tolerance test in diagnosing panhypopituitarism. In order to prevent adrenal insufficiency, both Ray (49) and Olivecrona (30) found it necessary to maintain their patients on 25 mgm. of cortisone daily. It is not necessary to administer DOCA, since hypophysectomy has no effect on the mineral corticoids. Salt metabolism is not altered.

The loss of gonadal function is also apparent in hypophysectomized patients. Urinary gonadotrophin excretion falls to zero. Rays male patients (49) developed testicular atrophy within a few weeks. The

females had cessation of menses. Elden (44) reports on a sixteen year old female who gradually lost axillary and pubic hair after hypophysectomy. The autopsy on this same girl showed atrophy of the uterus and adnexa. Replacement therapy with appropriate sexual hormones will prevent changes in gonadal function.

Diabetes insipidus usually occurs in the first week following hypophysectomy, but may be delayed twenty days. Some investigators (50) feel that the onset of polyuria is indicative of an incomplete hypophysectomy. However, Lipsett (57, 58) reported diabetes insipidus was present in 67% of Rays cases who had complete hypophysectomy. Many of these were proven to be complete by autopsy studies. Lipsett feels that the presence or absence of polyuria cannot be used as a criterion for determining the completeness of hypophysectomy. If the output exceeds 150 ml/hour, the patient is placed on nasal pitressin.

Hypophysectomy has no effect on blood pressure. In both Ray (49) and Olivecronas (30) series, the blood pressure showed no significant change following surgery.

Radon Seed Implantation

In the five cases in which radon seed implantation was performed, there were no deaths from the operative procedure itself. Although M. B. (case #3) died thirty-four days following surgery, her death was due to progression of her metastatic disease rather than to surgical complications.

Three patients had severe post-op headaches, but this usually subsided within a week. T. T. (case #2) developed visual and auditory hallucinations the first post-op week. E. B. (case #4) was troubled with nausea and vomiting, which disappeared after the administration of cortisone. K. P. (case #5) had a wound abscess that developed in an overlooked skin suture.

Two patients (#2 and 4) had visual disturbances following surgery. In both cases the onset was gradual, but progressed to the stage of almost complete blindness. It has been postulated that since the sella turcica and optic chiasma are in close proximity, the visual disturbance might be due to radiation damage. However, autopsy studies of E. B.'s brain showed metastatic tumor impinging on the optic tracts. T. T. had longstanding severe hypertension with retinopathy. The other three

cases had as large a total dosage of radiation to the pituitary and failed to show any loss of visual acuity. Thus, there is no clear cut evidence of radiation damage to the optic nerve. Histologic sections of the optic nerves and surrounding area were not available for this paper, so no conclusions can be drawn in this respect.

Significant objective remissions were seen in two of the five patients. K. P. (case #1) had a decrease in both the size and number of her metastatic lesions. Some of the skin nodules disappeared altogether. A. L. (case #5) also had a decrease in the size of her metastatic lesions. In addition, her chest x-ray showed evidence of disappearance of previously reported lung metastasis. All the patients had temporary decrease in the rate of progression of their neoplastic disease with the exception of M. B. (case #3). Her tumor was highly invasive and continued to spread unabated.

The duration of remission in K. P. (case #1) was three months. A. L. (case #5) showed no evidence of further progression for eighteen months. She also was receiving testosterone, which may have had some influence.

On two cases (#1 and 2), a second operation was performed, using a higher dosage the second time.

Neither had any further remission from the second procedure whatsoever. This seems to indicate that reoperation is of little value.

Judging from the general status of the patients at the time of radon seed implantation, their life expectancy was considerably prolonged. The length of survival following surgery varied from thirty-four days to twenty-two months with an average of fifteen months. A. L. (case #5) is still living, although in poor condition.

The best results were obtained subjectively. All the patients had some pain relief following radon seed implantation. This was especially apparent in K. P., who became quite euphoric. The relief from pain was out of proportion to objective changes in these patients. Three had significant relief of skeletal pain, while their x-rays showed no evidence of improvement.

Three of the patients were in such poor condition prior to surgery that they were unable to carry on any activities. After radon seed implantation, they were able to take care of their housework.

Radon seed implantation did not bring about the marked physiologic changes that are seen in surgical hypophysectomy. The target organs showed no evidence

of complete loss of hormonal stimulation from the pituitary gland. Pituitary function tests in these cases substantiated clinical observations.

E. B. (case #4) showed laboratory evidence of hypothyroidism. Her BMR fell from a /7% to a -35%. The radioactive iodine uptake was in the myxedematous range, with 6% uptake at the end of forty-eight hours. However, she showed no clinical evidence of myxedema. K. P. (case #1) showed a transient decrease in her basal metabolic rate, but radio active iodine uptake remained in the range of normal. None of the patients required thyroid replacement therapy.

17 keto steroid determinations were done periodically before and after radon seed implantation (see laboratory data). In none of the values obtained were there indications of decreased adrenal function. The adrenal glands were removed on K. P. a year following hypophysectomy. Microscopic sections reported normal adrenal tissue with no evidence of atrophy. None of the patients had an adrenal crisis. E. B. had a convulsive episode which was thought to be due to adrenal insufficiency. The finding of multiple cerebral metastasis on autopsy made this a more likely cause, in the presence of normal function tests. Some

of the patients were given 25 mgm. cortisone daily for variable periods of time. This was more for prophylactic reasons.

T. T. showed evidence of insulin hypersensitivity (chart #2) two months following surgery. The insulin tolerance test had to be discontinued at the end of one hour because of an insulin reaction. The following month, the test was repeated and no sensitivity was present. This same patient had an episode of convulsions, which may have been caused by hypoglycemia. Because of her condition, an insulin tolerance test was not attempted at that time.

There was no change in the serum protein or electrolytes in any of these patients following surgery. All the laboratory tests obtained were within the normal range. Thus, radon seed implantation does not upset the electrolyte or protein balance of the organism. The peripheral blood picture was also essentially unchanged.

It can be seen from the above findings that in none of these patients was pituitary function completely destroyed. It was apparently altered enough to upset the hormonal balance of the body, leading to either temporary cessation or slowing down of tumor growth.

Pituitary sections on K. P. (case #1) substantiate this conclusion. A longitudinal section of the gland (Figure 1) shows the necrotic anterior portion of the gland in the left upper portion of the photograph. Between the anterior pituitary and the stalk, a layer of dark stained cells can be seen, which are viable and functioning anterior pituitary cells. Figure #2 is a high powered magnification of this same area, showing the necrotic pituitary cells on the left and the viable cells on the right.

Two of the patients developed diabetes insipidus. The onset was more delayed than in surgical hypophysectomy. In both cases, it was over a month post-op before polyuria occurred. This was controlled by the use of nasal pitressin. In one patient the polyuria stopped spontaneously a few months later.

T. T. (case #2) had severe hypertension. The radon seed implantation did not lower the blood pressure, even in the immediate post-op period. From all indications, destruction of the pituitary has no effect on blood pressure.

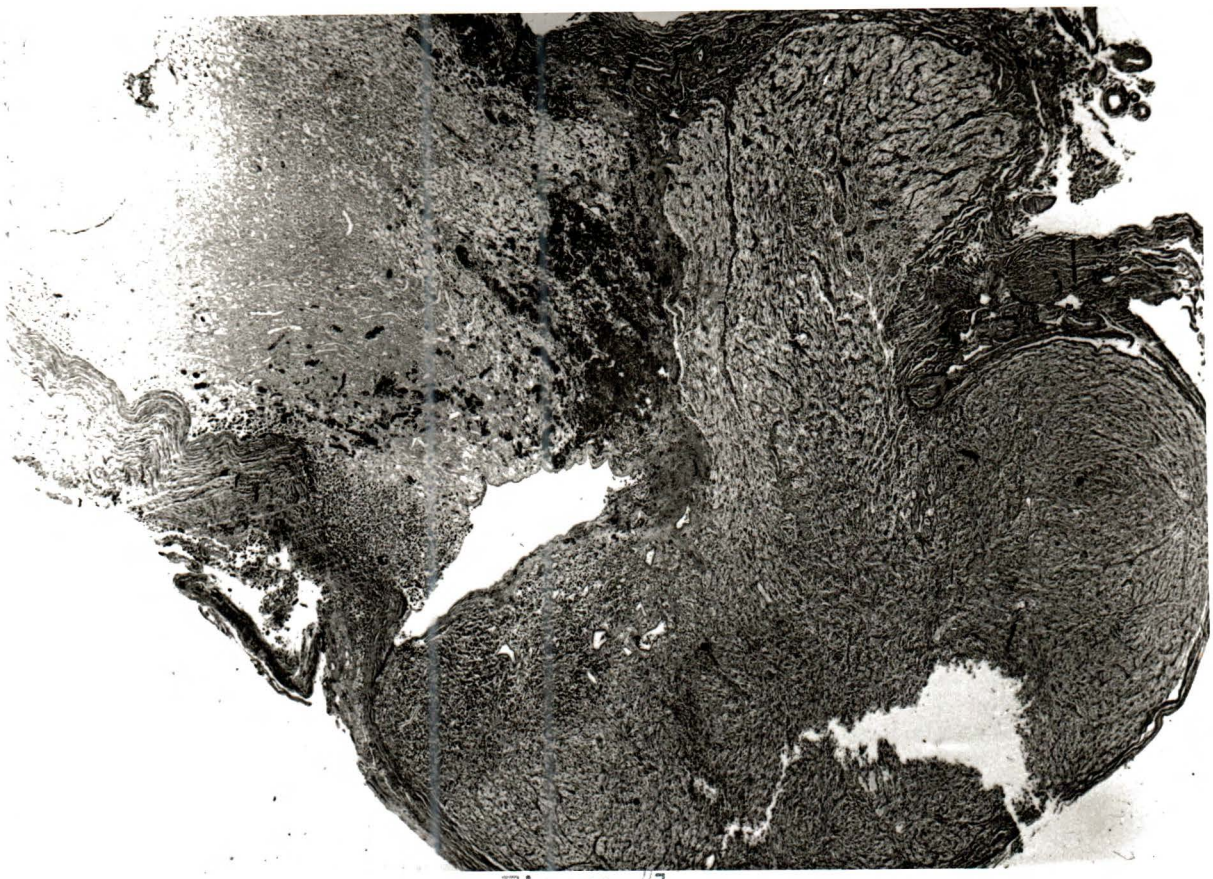

Figure #1

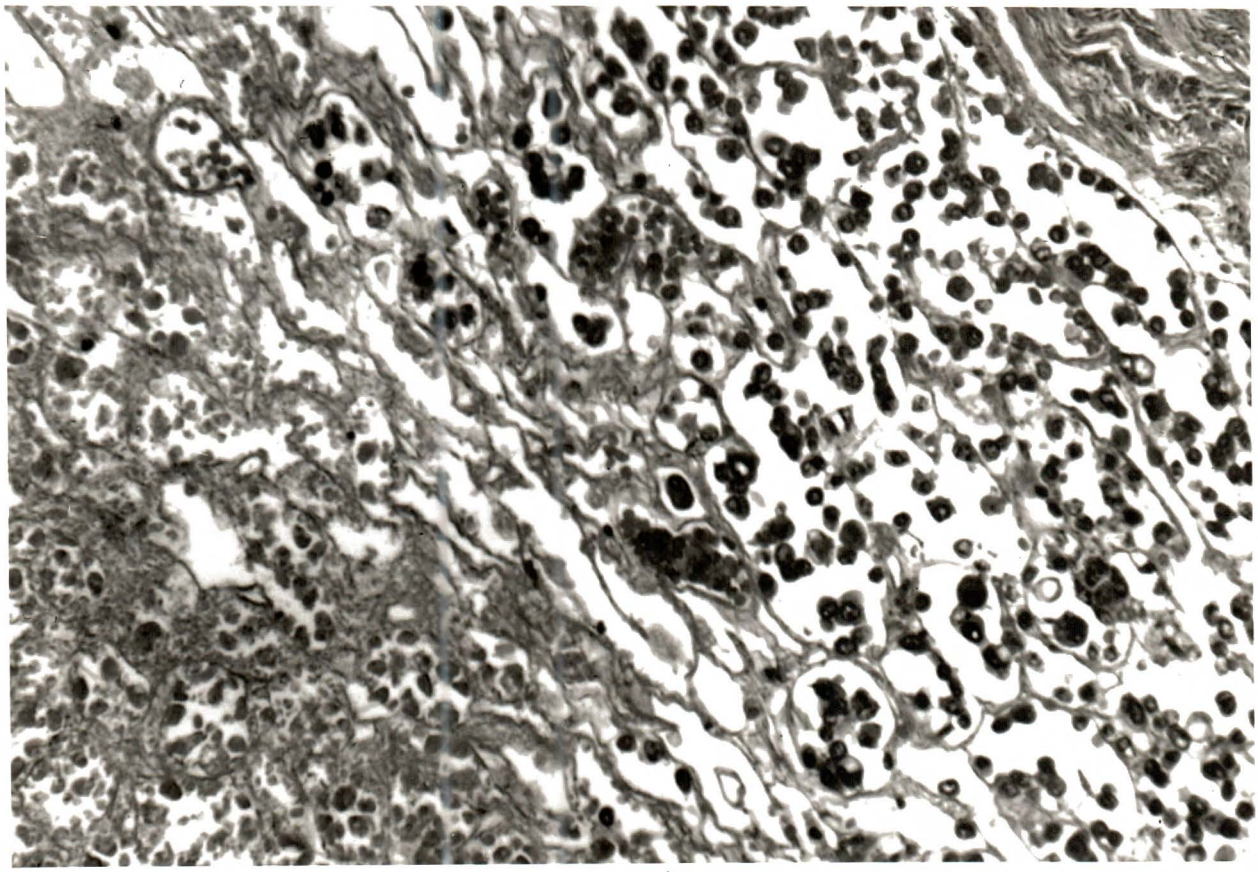

Figure #2

SUMMARY

Experimental studies in animals would indicate that the pituitary gland is related to the growth rate of certain neoplasms. Hypophyseal surgery has been attempted in several types of metastatic carcinoma, but has only met with success in carcinoma of the breast. Surgical removal has been the most successful method of inactivating the pituitary gland. Of the 116 cases of metastatic breast carcinoma reviewed, approximately 40% had a significant remission following hypophysectomy. All patients who had previously responded to oophorectomy gained a further remission from hypophysectomy. As high as 80% had some subjective relief of pain. Several tests, including 17 keto steroid and radio active iodine uptake values, will help determine the completeness of hypophysectomy.

Radon seed implantation performed in five cases at U.N.H., resulted in objective remission in two cases and subjective relief of pain in all five. Pituitary function tests indicated that none had complete destruction of the pituitary, which was substantiated in one case by the finding of viable anterior pituitary cells on autopsy.

CONCLUSIONS

1. Metastatic carcinoma of the breast is the only type of tumor in which hypophyseal surgery is beneficial.
2. Hypophysectomy under the best of conditions still only gives temporary remission, with the average remission expected to be approximately two years.
3. If complete removal of hormonal stimulation to the tumors is desired, there is reason to believe that hypophysectomy may be preferable to adrenalectomy.
4. Hypophysectomy is warranted in premenopausal women who have had previous remission from oophorectomy.
5. Radon seed implantation is a simpler procedure with less risk involved than surgical hypophysectomy. The morbidity rate of both is about the same.
6. In the hands of an experienced operator, the mortality rate from either procedure is surprisingly low in view of the patients condition.
7. The highest dosage of radon which should be used is 9 millicuries to avoid damaging the optic nerves.
8. Radon seed implantation does not result in complete loss of pituitary function as in surgical hypophysectomy.

BIBLIOGRAPHY

1. Crowe, S. J., Cushing, H. and Homans, J., Experimental Hypophysectomy, John Hopk. Hosp. Bull. 21, (1910.

2. Lisser, H., Hypophysectomy in Cushing's Disease, J. Nerv. and Ment. Dis. 99:727-733, 1944.

3. Pattison, A. R. D. and Swan, W. G. A., Surgical Treatment of Pituitary Basophilism, Lancet 1:1265-1269, (1938).

4. Ball, H. A. and Samuels, L. T., The Effect of Hypophysectomy on Transplanted Mammary Carcinoma in the White Rat, Am. J. Cancer 167351-359, 1932.

5. McEuen, C. S. and Thompson, D. L., The Effect of Hypophysectomy on the Growth of the Walker Rat Tumor, British J. Exper. Path. 14:384-91, 1933.

6. Korteweg, R. and Thomas, F., Tumor Induction and Tumor Growth in Hypophysectomized Mice, Am. J. Cancer 37:36-44, 1939.

7. Maurik, G. Van, Growth of a Transplantable Mammary Cancer in Continued Subpassages in Hypophysectomized Mice, Acta Physiol. Pharm. Neurl. 2:84-87, 1951.

8. Loeffler, J. B., Growth of Sarcoma in Hypophysectomized Rats, Cancer 5:161-162, 1952.

9. Gardner, W. W., Persistence and Growth of Spontaneous Mammary Tumors and Hyperplastic Nodules in Hypophysectomized Mice, Cancer Research 2:476-488, 1942.

10. Agate, F. J., Jr., Antopol, W., Glaubach, S., Agate, F. and Graff, S., The Nonessentiality of the Hypophysis for the Induction of Tumors with 3, 4-Benzyrene, Cancer Research 15:6-8, 1955.

11. Nagareda, C. S. and Kaplan, H. S., Effect of Hypophysectomy and X-Radiation on Lymphoid Organs and on the Induction of Lymphoid Tumors in C57BL Mice, Proc. Am. Assoc. Cancer Research 1:34-35, (April) 1954.

12. Moon, Henry D., Simpson, M. E., Effect of Hypophysectomy on Carcinogenesis: Inhibition of Methylcholanthrene Carcinogenesis, Cancer Research 15:403-406, (July) 1955.

13. Griffin, A. C., Rinfret, A. P. and Corsiglia, V. F., The Inhibition of Liver Carcinogenesis with 3-Methyl-4-dimethylaminazobenzene in Hypophysectomized Rats, Cancer Research 13:77-79, 1953.

14. Martinez, C., Bittner, J. J., Effect of Ovariectomy, Adrenalectomy and Hypophysectomy on Growth of Spontaneous Mammary Tumors in Mice, Proc. Soc. Exp. Biol., N. Y. 86:1. pp. 92-95, (May) 1954.

15. Noble, R. L. and Walters, J. H., The Effect of Hypophysectomy on 9, 10-Dimethyl-1, 2-benzathracine Induced Carcinogenesis, Proc. Am. Assoc. Cancer Research 1:35-36, 1954.

16. Richardson, H. L., The Role of Hormones in Azo Dye Induction of Liver Cancer and the Adrenal Lipoid Response in Hypophysectomized Rats, Cancer 7:1044-1047, (Sept.) 1954.

17. Griffin, A. C., Rinfret, A. P., Robertson, C. and O'Neal, M., Factors Involved in the Inhibition of Azo Dye Carcinogenesis by Hypophysectomy, Proc. Am. Assoc., Cancer Research 1:21-22, 1953.

18. Robertson, C. H., O'Neal, M. A., Griffin, A. C. and Richardson, H. L., Pituitary and Adrenal Factors Involved in Azo Dye Liver Carcinogenesis, Cancer Research 13:776-79, 1953.

19. Robertson, C. H., Further Observations On the Role of the Pituitary and the Adrenal Gland in Azo Dye Carcinogenesis, Cancer Research 14:549-553, (Sept.) 1954.

20. Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M., Neoplasms in Rats Treated with Pituitary Growth Hormone, I Pulmonary and Lymphatic Tissues, Cancer Research 10:297-308, 1950.

21. Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M., Neoplasms in Rats Treated with Pituitary Growth Hormone, V Absence of Neoplasms in Hypophysectomized Rats, Cancer Research 11:535-539, 1951.

22. Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M., Neoplasms in Rats Treated with Pituitary Growth Hormone, II Adrenal Glands, Cancer Research 10:364-370, 1950.

23. Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M., Neoplasms in Rats Treated with Pituitary Growth Hormone, III Reproductive Organs, Cancer Research 10:549-556, 1950.

24. Archer, B. J., The Incidence of Peripheral Malignancy in Simmonds' Disease with Special Reference to Cancer of the Breast, New York State J. Med. 53:328-329, 1953.

25. Scott, W. W., Role of Pituitary in Normal and Abnormal Prostatic Growth, Tr. Am. Ass. Genitourin. Surgeons 46:33-39, 1954.

26. Pearson, O. H., Ray, B. S., Harrold, C. C., West, C. D., Li, M. C., MacLean, J. P. and Pipsett, M. D., Hypophysectomy in the Treatment of Advanced Cancer, Tr. A. Am. Physicians 68:101-111, (1955).

27. Luft, R. and Olivecrona, H., Experiences with Hypophysectomy in Man., J. Neurosurg. 10:301-316, 1955.

28. Knowlton, A. I., Poll, J. L. and Jailer, V. W., Lack of Effect of Hypophysectomy Upon Metastatic Adrenocortical Carcinoma with Cushing's Syndrome: A Case Report, Journal of Clinical Endo. and Metabolism 14:205-214, Febr. 1954.

29. Shimkin, M. B., Boldrey, E. B., Kelly, K. H., Bierman, H. R., Ortega, P. and Naffziger, H. C., Effects of Surgical Hypophysectomy in a Man With Malignant Melanoma, J. Clin. Endocrinol. 12:439-453.

30. Luft, R. and Olivecrona, H., Hypophysectomy in Man, Cancer 8:261-270, (March-April) 1955.

31. Pearson, O. H., Ray, B. S., Harrold, C. G., West, C. D., Li, M. C., Effect of Hypophysectomy on Neoplastic Disease in Man, (abstr.) J. Clin. Endocrinal. 14:828, 1954.

32. Kennedy, B. J., Peyton, W. T. and French, L. A., Total Hypophysectomy in Advanced Breast Cancer, Bull. Univ. Minn. Hosp. and Minn. Med. Foundation 36:528-551, 1955.

33. Startebecker, J. D., Metastatic Tumors of the Brain, J. Neurosurg. 11:84-111, 1954.

34. Rothenberg, S. F., Jaffe, H. L., Putman, T. I., Simkin, B., Hypophysectomy with Radioactive Chronic Phosphate in Treatment of Cancer, A. M. A. Arch. Neur. Psychiat. 73:193-199, (Febr.) 1955.

35. LeBeau, J. and Perrault, M., Total Hypophysectomy in Treatment of Cancer, Semaine des Hospitaux de Paris 29:1093-1126, 1953.

36. Forrest, A. P., Brown, D. A., Pituitary Radon Implant for Breast Cancer, Lancet, Lond. 268: 1054-55, (May 21) 1955.

37. Russell, P. W., Hypophysectomy in Metastatic Breast Carcinoma, J. of Kansas Med. Soc. 56:481-485, (Sept., 55).

38. Luft, R., Olivecrona, H., Ikkos, D., Kornerup, T., Ljunggren, H., Hypophysectomy in Man; Further Experiences in Severe Diabetes Mellitus, Brit. M. J. 4942:752-6, (24 Sept. 55).

39. Kinsell, L. W. Lawrence, L., Balch, H. E. and Weyand, B. D., Hypophysectomy in Human Diabetes: Diabetes 3:358-366, (1955).

40. Luft, R., Olivecrona, H. and Sjogren, B., Hypophysectomy in Man: Experiences in Severe Diabetes, J. Clin. Endo. and Metab. 15:391-408, (1955).

41. Davidoff, L. M. and Feiring, M. D., Surgical Treatment of Tumors of the Pituitary Body, Am. J. Surg. 75:127-8, (1948).

42. Henderson, W. R., The Pituitary Adenomata; A Followup Study of Surgical Results in 338 Cases, Brit. Jour. Surg. 26:811.

43. Northfield, D. W. C., Radon Implantation for Acromegaly and Cushing's Syndrome, Proc. Roy. Soc. Med. 42:845-853, (1949).

44. Elden, C. A. and Kummer, A. J., A Clinical, Laboratory and Pathological Study of a Partially Hypophysectomized Human Female, J. of Clin. Endocrin. 3:596-599, (1943).

45. Albeaux-Fernet, M., Guiot, J., Braun, S. and Romain, J. D., Results of Surgical Hypophysectomy in a Case of Malignant Edematous Exophthalmos, Journal of Clinical Endo. and Metabolism 15:1239-54, (1955).

46. Kelly, K. H., Feldsted, E. T., Browne, R. F., Ortega, P., Bierman, H. R., B. V. A., Lombur and Shimkin, M. B., Irradiation of the Normal Human Hypophysis in Malignancy: Report of 3 cases Receiving 8,100-10,000 r Tissue Dose to the Pituitary Gland, V. S. National Cancer Institute Journal 11:967-983, 1951.

47. Rassmussen, T., Harper, P. V., Kennedy, T., The Use of a Beta Ray Point Source for Destruction of the Hypophysis, Surg. Forum 4:681-686, (Oct.) 1953.

48. Leicher, F., Hypophysial Changes Following Electrocoagulation, Arch. Kin. Chir. 278: 301-311, 1954. Abstract in J. A. M. A., Dec. 4, 1954, Vol. 156, No. 14.

49. Ray, B., Hypophysectomy in the Treatment of Breast Carcinoma, Interurban Neurosurgical Society Meeting, Febr., 1956.

50. Pearson, O. H., Li, M. C., MacLean, J. P., Lipsett, M. B. and West, C. D., Management of Metastatic Mammary Cancer, J. A. M. A. 159:1701-4, (Dec., 1955).

51. Pearson, O. H., Ray, B. S., West, C. D., Harrold, C. C., MacLean, J. P. and Li, M. C., Pituitary Somatopropin As a Growth Factor for Human Mammary Carcinoma, J. Clin. Invest. 33:956-957, 1954.

52. Li, M. C., Rall, J. E., MacLean, J. P., Lipsett, M. B., Ray, B. S. and Pearson, O. H., Thyroid Function Following Hypophysectomy in Man, J. of Clin. Endo. and Metab. 15:1228-37, (1955).

53. Fraser, R. and Smith, P. H., Simmonds' Disease or Panhypopituitarism (anterior), It's Clinical Diagnosis by the Combined Use of 2 Objective Tests, Quart. J. Med. N. S. 10:297-330.

54. Luft, R., Olivecrona, H., Sjogren, B., Ikkos, D. and Ljunggren, H., Therapeutic Results of Hypophysectomy in Metastatic Carcinoma of the Breast and in Severe Diabetes Mellitus; Adrenocortical Function after Hypophysectomy, Ciba Foundation Colloquia on Endocrinology, Vol. VIII, The Human Adrenal Cortex, London, J. and A. Churchill, Ltd., 1955. pp. 438-459.

55. Sheehan, H. L. and Summers, V. K., The Syndrome of Hypopituitarism, Quart. J. Med. 18:319-378, 1959.

56. Ikkos, D., Luft, R. and Olivecrona, H., Hypophysectomy in Man: Effect on Water Excretion During the First Two Postoperative Months, J. Clin. Endo. and Metab. 15:553-567, (1955).

57. Lipsett, M. B. and others, Analysis of the Polyuria Produced by Hypophysectomy in Man, J. Clin. Endocrinol. 15:843, (July, 1955).

58. Lipsett, M. B., MacLean, J. P., West, C. D., Analysis of Polyuria Induced by Hypophysectomy in Man, J. Clin. Endo. and Metab. 16:183-195, (1956).