ine, it was felt by many that the "active" hormone had finally been identified. It soon became apparent, however, that triiodothyronine is transported more rapidly into the peripheral tissues than is thyroxine and, furthermore, that the quantity of triiodothyronine formed from thyroxine *in vivo* is minute indeed. Support for this concept weakened. Triiodothyroacetic acid and tetraiodothyroacetic acid enjoyed a temporary popularity (17), but their candidacy for the "active" compound was abortive.

Although there still exists among some investigators a reluctance to accept thyroxine and triiodothyronine as the thyroid hormones active at the cellular level, there is no compelling reason to believe that any other unidentified "active" compound exists. Therefore, sixty-six years after Baumann's initial efforts, twenty-five years after the identification of L-thyroxine, and eight years after the identification of L-triiodothyronine, it seems that the case may rest.

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WILLIAM WALLACE SCOTT *and* HORST K. A. SCHIRMER

HYPOPHYSECTOMY FOR DISSEMINATED PROSTATIC CANCER

In September, 1948, hypophysectomy was performed for the first time in the treatment of disseminated prostatic cancer (1, 2, 3). This was unsuccessful, the patient surviving only eleven days. It was not possible to determine the completeness of removal clinically, and permission for an autopsy could not be obtained. No further attempts were made until November, 1951, by which time cortisone was readily available. In 1951 and 1952, with Doctor A. Earl Walker performing the surgery, five additional hypophysectomies were attempted. The favorable results observed in two patients in whom surgical removal of the pituitary was almost complete, coupled with evidence which implicates the pituitary in malignant growth, prompted us to continue our studies. This paper will consist of a presentation of the case histories of seventeen patients with advanced prostatic cancer in whom hypophysectomy has been carried out in this clinic, an evaluation of their response, and an analysis of the mechanisms which may be involved in this response.

METHODS AND MATERIALS

Between September 24, 1948, and January 17, 1961, seventeen patients with disseminated prostatic cancer were subjected to hypophysectomy.

WILLIAM WALLACE SCOTT is professor of urology, The Johns Hopkins University School of Medicine, and urologist-in-charge, The Johns Hopkins Hospital, Baltimore, Maryland.

HORST K. A. SCHIRMER is instructor in urology, The Johns Hopkins University School of Medicine, and urologist, The Johns Hopkins Hospital, Baltimore, Maryland.

All but two (Cases 1 and 2) had received at least one other form of endocrine therapy, such as castration, and all but two patients of the remaining fifteen (Cases 13 and 14) were judged to be in relapse and in great need of palliation.

With the exception of Case 2, hypophysectomy was performed via right frontal craniotomy, an approach which Bronson Ray (4) has found to be much superior to either a temporal or a transnasal, transphenoidal one. General anesthesia, usually sodium pentothal, has been used in all cases, and since 1958, hypothermia has proved to be a useful adjunct. In this series, with the exception of Case 14, no agent such as Zenker's solution, or any form of irradiation, was used in an effort to destroy residual pituitary tissue.

The substitution therapy for hypophysectomy as originally devised has been reported in detail elsewhere (3). More recently, Pearson *et al.* (4) have modified this therapy as have we when the need has arisen. With more experience it has become obvious that the need for replacement therapy depends upon the completeness of removal. When hypophysectomy is complete or nearly complete, all patients will require cortisone acetate in amounts of 25–50 mg. per day and desiccated thyroid in amounts of 64–128 mg. per day, both doses to be given orally. The dosage of cortisone should be increased during periods of stress; and some patients will require posterior pituitary powder in the form of snuff to control their thirst and polyuria. In our experience and in that of others (5), postoperative care is less difficult than after bilateral adrenalectomy, and the maintenance of fluid and electrolyte balance is straightforward.

In this study efforts have been made clinically in a number of cases to assess completeness of hypophysectomy by tests of thyroid function, including the basal metabolic rate, radioactive iodine studies, and serum cholesterol; by tests of altered carbohydrate metabolism, including fasting blood sugars and glucose tolerance tests; by observing the urinary output to detect the occurrence of diabetes insipidus; and by measuring urinary steroid excretion. Determinations of urinary gonadotrophins were not made, although the levels of such are considered by some investigators (6, 7) to be a reliable, direct method of measuring pituitary function.

Autopsies were permitted in seven of fourteen patients. At the time of this writing, completeness of hypophysectomy has been determined in four patients by serial section of the entire sella turcica after decalcification.

These results are described below, and it appears that this method is the only reliable one to date of determining if hypophysectomy is complete.

Anyone who has spent years attempting to evaluate hormonal therapy of such cancers as those of the prostate and breast fully recognizes the difficulties involved. These difficulties have been emphasized by the recent co-operative studies of breast and prostatic cancer sponsored by the Cancer Chemotherapy National Service Center of the National Cancer Institute. In such studies every effort has been made by authorities in the field to establish reliable protocols in order to learn which criteria are reliable indices of objective improvement. At least in the case of prostatic cancer it seems fair to state at this writing that few objective criteria have been established. Therefore, in presenting our results, we shall do so according to certain criteria which we have chosen, such as the level of serum acid phosphatase, the appearance of osseous metastases, etc., and let the final evaluation of such data rest until a later date when it may be possible to establish the value of the criteria used. Of course, were any form of hormonal therapy curative, this could be determined with ease. Thus the patient with proven prostatic cancer would become free of the signs and symptoms of the disease, such as an elevated serum acid phosphatase, osseous metastases, pain, weight loss, anemia, etc., and at autopsy, no cancer would be found. But when a procedure is palliative only, it becomes difficult at times to assess the degree of palliation.

CASE HISTORIES

CASE 1. J.K. This 69-year-old Negro male was admitted to the Johns Hopkins Hospital on August 11, 1948, having been referred by his family physician with a diagnosis of probable metastatic prostatic cancer. His chief complaints were a gradual decrease in size and force of his urinary stream and increasing frequency day and night, all of three years' duration. For two years he had suffered moderate to severe pain in his lower back and right hip. On physical examination the lumbar spine was tender to percussion, and on rectal palpation the prostate gland was two to three times enlarged, nodular, stony-hard and fixed, with extension into the left seminal vesicle.

Investigations. X-rays of the pelvis showed extensive osteoblastic changes throughout the lower lumbar spine, sacrum, and right ilium. Blood studies revealed a mild myelophthisic anemia, probably secondary to widespread osseous metastases, and an N.P.N. of 44 mg. per cent, falling to 25 mg. per cent before operation. Serum cholesterol was 260 mg. per cent, and a glucose tolerance test was normal. Serum phosphatases were: acid, 3.8 King and Armstrong units; alkaline, 52.6 King and Armstrong units. Open perineal biopsy revealed adenocarcinoma of the prostate. A satisfactory B.M.R. was +16.

Treatment and course. On September 24, 1948, hypophysectomy via frontal craniotomy (Dr. A. Earl Walker) and bilateral testicular biopsy were performed under general anesthesia. Histological examination of the testes revealed tubular hypoplasia and atrophy, and a relative increase in interstitial cells.

During the operation and the immediate postoperative period the vital signs remained stable except for a short-lasting hypotensive episode. Deoxycorticosterone acetate was given with return of the blood pressure to normal. Polyuria and polydipsia were not observed. Serum electrolytes stayed within normal limits but blood sugar levels fell. A marked hypoglycemic glucose tolerance curve was noted. The patient died in hypoglycemia on the eleventh postoperative day. His blood sugar was 16 mg. per cent, N.P.N. 25 mg. per cent, and serum cholesterol 132 mg. per cent. Permission for autopsy was refused.

Clinical evaluation. In our opinion, the patient did not survive hypophysectomy long enough to permit either a subjective or objective evaluation.

CASE 2. G.W. This 74-year-old Negro male was admitted to the Johns Hopkins Hospital on October 10, 1951, having been referred from the Medical Clinic with a diagnosis of probable metastatic prostatic cancer. His chief complaints were those of infravesical urinary obstruction of two years' duration, pain in his left temporal region, and weakness of his upper eyelid resulting in complete ptosis and diplopia, all of about two months' duration. During the previous six months he had lost twenty pounds in weight and on admission complained of low back pain, progressive anorexia, and constipation. On examination he appeared chronically ill. B.P. 120/64. Abnormal findings were a dilated, fixed left pupil, left exophthalmos and paralysis of the third, fourth, and sixth cranial nerves on the left side. There was tenderness over the right costovertebral angle. The inguinal lymph nodes were enlarged, firm, and fixed bilaterally. On rectal examination the prostate gland was moderately enlarged, stony-hard, nodular, fixed, with lateral extension to the right and left.

Investigations. X-rays revealed a tumor metastasis in the right seventh rib associated with pleural metastases and possible metastases to the eighth thoracic and second lumbar vertebrae. Blood studies revealed a hematocrit of 35 per cent, a serum acid phosphatase of 3.8 Bodansky units, a serum cholesterol of 237 mg. per cent, and N.P.N. values ranging from 46 to 32 mg. per cent. Two satisfactory B.M.R. determinations were +20 and +14; and an ACTH test and glucose tolerance test were normal. Preoperative urinary 17-ketosteroids ranged from 6 to 8 mg. per 24 hours.

Treatment and course. On November 16, 1951, hypophysectomy and left retrogasserian neurectomy via frontal craniotomy were performed under general anesthesia by Dr. A. Earl Walker. The patient tolerated the procedure well and his postoperative course was essentially uneventful except for moderate, short-lasting diabetes insipidus. By the thirty-fifth postoperative day he was entirely free of pain, and on rectal examination remarkable regression of the prostate was noted. Serum acid and alkaline phosphatase values fluctuated from time to time but except toward death remained elevated and above prehypophysectomy values. On repeat X-ray examination of the bones, it was felt that the lesions seen preoperatively remained unchanged, but a few new lesions became manifest several months after hypophysectomy. The B.M.R. fell to +6, and a radioiodine slope of 0.11 was interpreted as being in the hypothyroid range. All postoperative urinary 17-ketosteroids were lower than preoperative ones and by the fourth to the fifth week ranged from 2 to 3 mg. per 24 hours. After long and extensive postoperative study he was discharged from the hospital in excellent clinical state, maintained on 25 mg. of cortisone acetate per day.

The patient was readmitted to the hospital on April 21, 1952, because of right lower quadrant pain suggestive of acute appendicitis, drowsiness, fever, and a white blood count of 13,400. Exploratory laparotomy was performed the following day, revealing a normal appendix but massive infarction of a large metastasis in a right pelvic lymph node. The abdomen was closed. On the fourth postoperative day, while up for the first time, the patient suddenly expired from what proved at autopsy to be a massive pulmonary embolism (April 26, 1952).

The anatomical diagnosis consisted of carcinoma of the prostate, with invasion of the urinary bladder, metastases to pelvic lymph node, vertebra, sella turcica and liver, recent massive infarction of a large metastasis in the right pelvic lymph node. There was evidence of atrophy of the prostate, atrophy of the adrenal cortex, pulmonary emphysema, bilateral fibrous pleural adhesions, and calcified primary tuberculous complex. The cause of death was a massive pulmonary embolus.

Serial sections through the sella turcica were examined by Dr. A. Earl Walker. He states: "Roughly one might estimate that approximately 12 per cent of the pituitary gland by volume is present and in the specimen. The majority of this tissue was viable."

Clinical evaluation. In our opinion, this patient received marked subjective benefit from hypophysectomy. However, objective signs, such as lowering of serum acid phosphatase and improvement in osseous metastases, were not observed.

CASE 3. B.S. This 66-year-old white male was admitted to the Johns Hopkins Hospital on February 19, 1952, having been referred by his urologist for further treatment of disseminated prostatic cancer. Three years prior to admission he experienced progressively severe low back pain for which bilateral orchiectomy was performed in September, 1950. This afforded some relief. In February, 1951, stilbestrol was begun with some relief of pain for six months. On admission he complained of severe pain in the shoulders, ribs, lumbar spine, and lower extremities, and of severe anorexia and a loss of thirty-five pounds in weight. Urinary obstructive symptoms were minimal. On examination the patient appeared pale and in poor nutritional state. Bilateral gynecomastia was noted. The heart was enlarged, exhibited extrasystoles, and was insufficient—with liver engorgement and ankle edema. On rectal palpation the prostate gland was small but stony-hard, nodular, fixed, with lateral extension of the induration.

Investigations. X-rays of the skeleton revealed widespread osseous metastases to the lumbar spine, pelvis, ribs, and pectoral girdle. The right lung showed metastases on chest X-ray. Blood studies revealed an anemia for which he was transfused, a normal N.P.N., and marked elevation of his serum acid and alkaline phosphatases. His B.M.R. was +26, and a glucose tolerance curve was diabetic. An intravenous pyelogram showed no func-

tion in 20 minutes on the right, and an EKG disclosed auricular fibrillation and coronary insufficiency. Urinary 17-ketosteroids ranged close to 4 mg. per 24 hours.

Treatment and course. On March 11, 1952, hypophysectomy was performed through a right frontal craniotomy under general anesthesia by Dr. A. Earl Walker. The patient withstood the procedure well. Mild hypotension required stimulants, but by the fifth postoperative day the patient was afebrile, normotensive, and ambulatory. Mild, short-lasting diabetes insipidus was noted. However, without question, his course was a continuously downhill one until death. Relief of pain was slight. After one week at home he was readmitted in an almost comatose, hypotensive, anemic condition, and with a fever of 103 degrees. An EKG showed a right bundle branch block and suggested hyperkalemia. In spite of supplemental steroid therapy, he became anuric and died in shock on April 14, 1952, one month and three days posthypophysectomy. Autopsy revealed saturation metastases, including the adrenals and remaining hypophysis. Based on serial sections of the sella turcica Dr. A. Earl Walker stated: "Approximately 30 to 35 per cent of the pituitary gland remains in the sections. There is rather marked inflammatory reaction about the dura mater and numerous clumps of carcinoma cells."

Clinical evaluation. In our opinion, this patient experienced no subjective or objective benefit from hypophysectomy.

CASE 4. J.B. This 47-year-old Negro male was readmitted to the Johns Hopkins Hospital on February 26, 1952. For two years he had experienced lower urinary tract obstructive symptoms. On December 19, 1951, because of these symptoms, a stony-hard prostate and an elevated serum acid phosphatase, he underwent transurethral resection and bilateral orchiectomy, performed by Dr. J. A. Campbell Colston. Sections of the tissue removed revealed poorly differentiated prostatic carcinoma. Stilbestrol therapy was initiated. Between December 19, 1951, and April 1, 1952, his course was one of repeated evacuations, fulgurations, and catheter drainage. Hematology consultation revealed no increase in fibrinolysin and a normal fibrinogen. No symptoms of metastases developed. On physical examination, pathologic findings were confined to the prostate gland, which was three to four times enlarged, stony-hard, nodular, and fixed, with extension laterally on both sides.

Investigations. An X-ray bone survey revealed nothing to suggest prostatic cancer metastases, but the floor and anterior surface of the sellar dorsum appeared to be eroded. During the two-week period prior to hypophysectomy, serum acid phosphatases ranged from 0.7 to 9.2 Bodansky units, alkaline phosphatases from 3.7 to 5.6 Bodansky units, hematocrits from 32 to 35.6 per cent, N.P.N. values from 20 to 27 mg. per cent, and urinary 17-ketosteroids from 4 to 6 mg. per day. A B.M.R. was +6, and two glucose tolerance tests were normal.

Treatment and course. On April 1, 1952, hypophysectomy was performed under general anesthesia via a right frontal craniotomy by Dr. A. Earl Walker. Unfortunately, anatomic considerations made it impossible to get a good look at the pituitary, and Dr. Walker felt that extirpation was not complete. Remarkable findings in the immediate postoperative period were euphoria, epigastric distress associated with nausea and vomiting, and a mild

hypoglycemia. At the time of discharge, May 5, 1952, from this admission, his general condition was fair. Except for one determination, his serum acid phosphatases remained elevated. His prostate gland was felt by three examiners to be somewhat smaller and less firm. He was readmitted three times to this hospital before death on January 11, 1953. During October, 1952, a diagnosis of gastric ulcer secondary to cortisone replacement therapy was made. Such was not found at autopsy. He developed progressive uremia, which was thought to be secondary to lower ureteral obstruction from prostatic cancer, and died in uremic coma January 11, 1953, nine months and eleven days after hypophysectomy. At autopsy, tremendous local growth of the prostatic cancer was observed, with metastases to lungs and many lymph nodes, but with no gross involvement of the bones. Regarding completeness of removal of the pituitary, Dr. Walker stated: "Although it is impossible to estimate the amount of tissue remaining with any degree of accuracy, it seems probable that from one-third to one-half of the gland must have been spared."

Clinical evaluation. In our opinion, this patient experienced little, if any, subjective or objective benefit from hypophysectomy, which was grossly incomplete.

CASE 5. N.K. This 60-year-old white male was readmitted to this hospital on October 8, 1952, for consideration of hypophysectomy in the treatment of his disseminated prostatic cancer. Three years earlier he had begun to experience lower urinary tract obstructive symptoms associated with some low back pain. A diagnosis of adenocarcinoma of the prostate was established by perineal prostatic biopsy and subsequent transurethral resection for prostatic obstruction (October 7 and 14, 1949). At this time X-rays of the bones were negative and serum phosphatases normal. On September 7, 1951, a second transurethral resection was performed for relief of obstruction. Bilateral orchiectomy was done at the same time, because the prostatic cancer had not seemed to shrink on estrogen therapy during the previous twelve months. Response to castration was judged to be favorable for ten months. However, by August, 1952, the patient was suffering with severe pain in the right shoulder. Biopsy of a scapular lesion seen on X-ray revealed metastatic prostatic cancer. Irradiation therapy was ineffectual. He had lost much weight and appeared chronically ill.

Investigations. X-rays of the bones revealed a marked extension of the osteoblastic lesion in the right acromion process, and although the pelvis X-rays were technically poor, the remainder of the bones appeared normal. Serum acid phosphatase levels ranged from 7.2 (probably in error) to 46.5 and 47.0 Bodansky units, respectively. Hemoglobin ranged from 11.5 to 12.5 g., N.P.N. values from 30 to 32 mg. per cent, a B.M.R. was +15, and a glucose tolerance test was normal.

Treatment and course. On October 24, 1952, Dr. A. Earl Walker conducted hypophysectomy via right frontal craniotomy. The immediate postoperative course was characterized by fever, sanguinous rhinorrhea, hyperglycemia, deep coma, generalized edema, and pulmonary congestion. This was followed by hypovolemia, hypotension, and oliguria. The patient expired on the third postoperative day (October 26, 1952). Permission for autopsy could not be obtained.

Clinical evaluation. In our opinion, this patient died as a result of the operation. No subjective or objective benefit from hypophysectomy was obtained.

CASE 6. W.B. This 66-year-old Negro male was readmitted to the Johns Hopkins Hospital on October 5, 1952, with a two-year history of low back pain with sciatic radiation, lower urinary tract obstructive symptoms, and a recent history of periodic nausea, vomiting, and dizziness. At an earlier admission in 1950, a diagnosis of disseminated prostatic cancer had been made on the basis of a palpably enlarged, hard prostate gland, X-ray evidence of osseous metastases, and marked elevation of serum acid and alkaline phosphatases—both as high as 60–80 Bodansky units. With the possible exception of slight lowering of the serum acid phosphatase, little improvement was noted upon administration of 200–1200 mg. per day of *p*-hydroxypropiophenone for thirty-six days. He then received stilbestrol, 3 mg. per day for one month, which relieved his bone pain and caused a precipitous fall in serum acid phosphatase from 82.8 to 2.5 Bodansky units. Castration was performed on June 8, 1951, and for the next sixteen months the patient continued to take stilbestrol intermittently. A good response was observed for twelve months. However, by October, 1952, the patient was experiencing severe pain in his left thigh and lower leg, associated with severe lymphedema of both legs. He also gave an interval history suggestive of a mild stroke. On examination a mass was palpable in the right upper quadrant. The extremities were involved in edema, and the prostate gland was still enlarged, stony-hard, nodular, and fixed.

Investigations. X-ray examination again revealed osseous metastases, with some suggestion of healing in some areas and progression and new metastases in others. Prior to hypophysectomy, serum acid phosphatases ranged from 2.2 to 3.7 Bodansky units, serum alkaline phosphatases from 48.4 to 80.1 Bodansky units, N.P.N. values from 25 to 37 mg. per cent, and urinary 17-ketosteroids averaged close to 9.0 mg. per 24 hours. Two B.M.R. determinations were both +44, and two glucose tolerance tests were mildly diabetic.

Treatment and course. On November 4, 1952, hypophysectomy was performed via a right frontal craniotomy by Dr. A. Earl Walker. This was well tolerated. During the course of the next six weeks the patient's lymphedema disappeared, he gained weight, and his pain disappeared. Whereas his serum acid phosphatase stayed down, there was little change in his alkaline phosphatase. The B.M.R. fell to −5, and urinary 17-ketosteroids to an average of 4.0 mg. per 24 hours. Between August 4, 1953, and his death on November 27, 1953, he was admitted to the hospital three times. Each time it was necessary to regulate his electrolytes probably because the patient failed to take his cortisone regularly. During August, 1953, X-rays of the skeleton showed a decrease in the extent and density of osseous metastases; the prostate gland showed moderate to marked regression in size and induration. Also, an aneurysm of the right carotid artery was detected. On November 21, 1953, the patient became lethargic and was admitted to the hospital in uremia with an N.P.N. of 101 mg. per cent. He gradually became comatose and died on November 27, 1953. The cause was somewhat obscure. The clinical picture suggested a cerebrovascular accident, adrenal insufficiency, and hypothyroidism. The patient survived hypophysectomy one year and twenty-three days.

An autopsy was performed. Serial section examination of the contents of the sella turcica by Dr. A. Earl Walker suggested: "The pituitary tissue remaining is about 5 per cent of the total pituitary."

Clinical evaluation. In our opinion, this patient experienced subjective and objective benefit from hypophysectomy for almost one year.

CASE 7. J.H. This 56-year-old white male was readmitted to the Johns Hopkins Hospital on October 30, 1958, for further treatment of disseminated prostatic cancer. During September, 1956, the patient began to experience lower urinary tract obstructive symptoms and dull aching pain in his left hip. A stony-hard, enlarged, fixed prostate gland suggested prostatic cancer, and his urologist, Dr. Austin Wood, initiated stilbestrol therapy which afforded symptomatic improvement for several months. In January, 1957, obstructive symptoms recurred, necessitating transurethral resection. Sections revealed prostatic adenocarcinoma. He was first admitted to this hospital on August 8, 1957, complaining of severe left hip pain, which prevented him from working. Serum phosphatases were elevated, but no definite metastases were seen on X-ray. Bilateral orchiectomy was performed on August 12, 1957, from which he obtained fair but short-lasting relief of pain. Meticorten, 10 mg. per day, and large doses of stilbestrol seemed to help for a while, but by mid-September, 1958, the patient was suffering very severe pain in the left hip and leg. X-rays now showed marked osteoblastic metastatic involvement of the pubic and ischial bones bilaterally with extension into the left acetabulum. In mid-October, 1958, X-ray therapy was directed to the left hip for seven treatments, with relief of pain for about ten days. On admission on October 30, 1958, the pain in his left leg was again intractable and its motor power almost gone. Admission was for the purpose of cordotomy or hypophysectomy.

On this physical examination he appeared to be undernourished and in acute distress. His color was pale, and scattered ecchymoses were present over both forearms, noted since Meticorten therapy was initiated. The lower extremities were involved in marked lymphedema, and neurologic examination disclosed markedly decreased motor power in both legs, especially in the left. Deep tendon reflexes were somewhat depressed. On rectal examination the prostate gland was felt to be only minimally enlarged, with moderate induration of the left lateral lobe, fixation, and some lateral extension.

Investigations. X-rays of the bones again revealed findings very much like those described above. More extensive studies were done on the urinary steroids, employing silica gel column fractionation and infrared analysis. Preoperatively, the following values, expressed in mg. per 24 hours, were observed: crude neutral, 8.4; total ketonic, 4.8; alpha ketonic, 2.1; androsterone, 0.32; etiocholanolone, 0.51; androsterone/etiocholanolone ratio, 0.63; 11-ketoetiocholanolone, 0.25; 11-hydroxyandrosterone, 0.13; 11-hydroxyetiocholanolone, 0.15; and androgen/corticoid ratio, 1.56.

Treatment and course. On November 3, 1958, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. David S. Rasmussen-Taxdal. The patient withstood the procedure extremely well. Moderate diabetes insipidus was observed for six days. On discharge from the hospital on November 30, 1958, about four weeks after hypophysectomy, the patient was able to walk, his leg pain was minimal, and the lymphedema of both extremities was gone. Repeat analysis of urinary 11-deoxy- and 11-oxy-17-ketosteroids one month after hypophysectomy revealed the following values, expressed in mg. per 24 hours: crude neutral, 8.2; total ketonic, 1.9; alpha ketonic,

1.5; androsterone, 0.7; etiocholanolone, 0.34; androsterone/etiocholanolone ratio, 0.50; 11-ketoetiocholanolone, 0.43; 11-hydroxyandrosterone, <0.05; 11-hydroxyetiocholanolone, 0.18 and androgen/corticoid ratio, 0.84. Examination seven months after hypophysectomy revealed a weight gain of twenty-five pounds, freedom from pain, and a change in the nature of the pelvic metastases from lytic to blastic. Thyroid replacement therapy was increased because of hypothyroid slope on iodine uptake studies. Cortisone was continued at 50 mg. a day.

By July, 1960, pain and weakness of his left leg had recurred and within one month he was paraplegic. He was readmitted to this hospital on August 20, 1960, as an emergency with marked shortness of breath and anemia. Even though it was felt that the patient was in impending congestive heart failure, it was decided to begin transfusion of half units of packed red cells because of the severe anemia (hematocrit, 20 per cent). Although maintained on a standard routine for congestive failure, he expired a few hours later, surviving hypophysectomy for almost twenty-two months.

Permission for autopsy was obtained, but at this writing serial sections of the sella turcica have not been examined in order to determine completeness of hypophysectomy.

Clinical evaluation. In our opinion, this patient experienced subjective and objective benefit for about eighteen months following hypophysectomy.

CASE 8. A.F. This 69-year-old Negro male was readmitted to the Johns Hopkins Hospital on November 23, 1958, with an almost complete paralysis of his lower extremities secondary to metastatic prostatic cancer. He was first seen here in August, 1953, because of lower urinary tract obstructive symptoms. By November, 1954, a diagnosis of disseminated prostatic cancer had been established on the basis of rectal findings, perineal punch biopsy (adenocarcinoma of the prostate), markedly elevated serum acid phosphatase, and saturation osteoblastic metastases. Castration was performed and the patient was placed on stilbestrol, 1 mg. three times daily. This therapy appeared to relieve his urinary symptoms. He remained quite well until the spring of 1958, at which time weakness of his legs caused him to discontinue work. By September, 1958, he had experienced a return of his lower urinary tract obstruction, had pain in his left knee and both shoulders, and had lost ten pounds in six months. During November, 1958, after evaluation by the Prostate Cancer Study Group, and in spite of additional stilbestrol therapy, he continued to worsen and was found to have almost complete paralysis of both legs, generalized cachexia, urinary retention, and marked elevation of both serum acid and alkaline phosphatases. On physical examination there was evidence of marked arteriosclerosis. The prostate gland was two times enlarged, stony-hard, fixed, and both seminal vesicles were indurated.

Investigations. X-rays revealed diffuse osteoblastic lesions in the pelvis and thoracolumbar spine. An admission hematocrit was 33 per cent, and serum acid and alkaline phosphatases were 18.9 and 125.4 Bodansky units, respectively. Iodine uptake studies revealed euthyroidism.

Treatment and course. On December 2, 1958, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. David S. Rasmussen-Taxdal. The procedure itself was well tolerated, but on the fifth postoperative day

the patient developed symptoms and signs of a hypothalamic infarct and died two days later of respiratory arrest (December 8, 1958). An autopsy was not permitted.

Clinical evaluation. In our opinion, it was obvious that death was caused by a complication incident to hypophysectomy.

CASE 9. L.F. This 59-year-old white male was readmitted to the Johns Hopkins Hospital on January 5, 1959. In November, 1956, a diagnosis of inoperable prostatic cancer was entertained on the basis of back pain and rectal palpation of the prostate. Serum phosphatases and skeletal X-rays were normal. On November 28, 1956, castration was performed, resulting in relief from pain until September, 1958, at which time he again experienced back pain with radiation into both lower extremities. Serum phosphatases were now elevated, and diffuse osteoblastic metastases were present on skeletal survey. On October 6, 1958, a transurethral resection of the prostate provided a positive tissue diagnosis of poorly differentiated adenocarcinoma. This patient then became a part of the co-operative study of prostatic cancer, and in the first double-blind trial received a placebo without benefit. Gradually his condition became worse as he developed pain, weakness, lymphedema of both legs, and generalized cachexia. On examination paroxysmal tachycardia, slight enlargement of the thyroid, and mild exophthalmos suggested mild hyperthyroidism. There was a marked decrease in motor power of both legs. The prostate was felt to be moderately enlarged, markedly indurated, fixed, with marked lateral extension.

Investigations. X-rays of the skeleton revealed widespread osteoblastic metastases with little change when compared with films made three months before. Admission phosphatases were: acid, 48.3 Bodansky units; alkaline, 26.3 Bodansky units. The N.P.N. was 18 mg. per cent and the hematocrit 37 per cent. A protein-bound iodine determination was 13.0 μg/100 ml serum (normal range =4.0–8.0 μg/100 ml). Qualitative and quantitative analysis of urinary steroids revealed the following values in mg. per 24 hours: crude neutral, 6.8; total ketonic, 6.2; alpha ketonic, 5.4; androsterone, 1.12; etiocholanolone, 1.63; androsterone/etiocholanolone ratio, 0.69; 11-ketoetiocholanolone, 0.40; 11-hydroxyandrosterone, 0.16; 11-hydroxyetiocholanolone, 0.36; and the androgen/corticoid ratio, 3.0.

Treatment and course. On January 9, 1959, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. David S. Rasmussen-Taxdal. The patient tolerated the procedure well, and his course in the hospital was quite uneventful. He was discharged on January 26, 1959, on 50 mg. per day of cortisone. Soon he became ambulant, free of pain, and began to gain weight. Serum acid phosphatase levels fell to below 1.0 Bodansky unit, and alkaline phosphatases dropped, but not to normal. Several observers felt that the prostate gland shrank considerably. Repeat studies of urinary steroids revealed the following values, expressed in mg. per 24 hours: crude neutral, 11.5; total ketonic, 4.5; alpha ketonic, 3.7; androsterone, 0.46; etiocholanolone, 0.62; 11-hydroxyandrosterone, <0.05; 11-hydroxyetiocholanolone, 0.20; and the androgen/corticoid ratio, 0.80. When last seen as an outpatient on December 10, 1959, eleven months after hypophysectomy, he was completely free of pain, had gained weight, and felt well generally. Serum phosphatases were: acid, 1.2 and alkaline 7.1 Bodansky units.

A bone survey revealed no significant change in the metastatic osteoblastic involvement. On December 30, 1959, he was brought by ambulance to this emergency department and pronounced dead on arrival. A coronary thrombosis was believed to have been responsible. An autopsy was performed and revealed prostatic cancer metastatic to bladder, bone, lymph nodes, adrenal, and liver, a fusiform aneurysm of the abdominal aorta with mural thrombus, and a posterior myocardial infarct. Serial sections of the sella turcica have not been reviewed at this writing.

Clinical evaluation. In our opinion, this patient experienced subjective and objective benefit for about ten months following hypophysectomy.

CASE 10. E.L. This 59-year-old white male was readmitted to the Johns Hopkins Hospital on February 9, 1959, complaining of intractable pain radiating into both legs. On the first admission, November 28, 1958, his complaints were essentially the same, and a clinical diagnosis of disseminated prostatic cancer was made based on rectal examination and the appearance on X-ray of widespread osteoblastic metastases. Serum phosphatases were: acid, 0.9 and alkaline, 19.6 Bodansky units. An intravenous pyelogram demonstrated a left hydroureteronephrosis, elevation of the bladder base, and a filling defect near the left ureterovesical junction. Castration was performed on December 1, 1958, and stilbestrol therapy, 500 mg. per day, was initiated. He failed to respond to these measures. On admission he was extremely pale and showed signs of weight loss (24 pounds in 2 months). He complained bitterly of back pain with radiation into both legs, and both legs were involved in marked lymphedema. Injections of morphine, $\frac{1}{4}$ grain every 4 hours, failed to relieve his pain, nor did codeine and aspirin taken between injections of morphine. Other findings were: bilateral gynecomastia, exquisite tenderness in the right-upper quadrant, and a small but hard, fixed, nodular prostate.

Investigations. Skeletal X-rays were not repeated during this admission. Serum phosphatases were: acid, 1.9 and alkaline, 28.2 Bodansky units. Hematocrit was 37 per cent. Protein-bound iodine was 5.7 μg. per 100 ml. An open perineal prostatic biopsy was performed on February 13, 1959, and confirmed the diagnosis of prostatic carcinoma with squamous metaplasia. Values for urinary steroids expressed in mg. per 24 hours were: crude neutral, 4.8; total ketonic, 1.7; alpha ketonic, 1.3; androsterone, 0.27; etiocholanolone, 0.22; androsterone/etiocholanolone ratio, 1.23; 11-ketoetiocholanolone, 0.20; 11-hydroxyandrosterone, 0.10; 11-hydroxyetiocholanolone, 0.12; and androgen/corticoid steroid ratio, 1.16.

Treatment and course. On February 16, 1959, hypophysectomy via frontal craniotomy under general anesthesia and hypothermia was performed by Dr. David S. Rasmussen-Taxdal. An extensive osseous metastasis was noted in the calvarium, which on section revealed undifferentiated carcinoma. Removal of the pituitary was thought to be complete. The immediate postoperative course was benign except for mild, short-lasting diabetes insipidus. However, on the fourteenth postoperative day, after having become free of pain, ambulatory, and without edema, the patient became confused, and six days later, he presented classical signs and symptoms of meningitis with septicemia secondary to chronic sinusitis. This necessitated a radical frontal and ethmoid sinus removal. Pneumonia, pulmonary atelectasis, pleural effusions, thrombocytopenia, and adrenal insufficiency

complicated the further postoperative course, and death occurred May 11, 1959, almost three months after hypophysectomy. At two months posthypophysectomy, serum phosphatases were: acid, 1.0 and alkaline, 14.7 Bodansky units. Repeat X-rays demonstrated no change in osseous metastases, but on rectal examination there was a marked reduction in the size and induration of the primary prostatic growth. Postoperative values for urinary steroids expressed in mg. per 24 hours were: crude neutral, 10.8; total ketonic, 1.7; alpha ketonic, 1.0; androsterone, 0.18; etiocholanolone, 0.2; androsterone/etiocholanolone ratio, 0.90; 11-ketoetiocholanolone, 0.12; 11-hydroxyandrosterone, <0.05; 11-hydroxyetiocholanolone, <0.05; and androgen/corticoid steroid ratio, 3.16.

An autopsy was performed, but at this writing serial sections of the sella turcica have not been examined in order to determine completeness of removal.

Clinical evaluation. In our opinion, death was almost surely secondary to a complication of hypophysectomy, but this patient experienced subjective and objective benefit from the procedure.

CASE 11. F.J. This 62-year-old Negro male was readmitted to the Johns Hopkins Hospital on February 18, 1959, for further treatment of his prostatic cancer. He was first admitted to this hospital in November, 1955, for this complaint, at which time he suffered low back pain, weight loss, and lower urinary tract obstructive symptoms. His serum acid phosphatase was 3.5 Bodansky units, his vertebrae were thought to harbor metastases, and a transurethral resection biopsy of the prostate revealed poorly differentiated adenocarcinoma. Castration was performed on November 23, 1955, but failed to relieve his back pain. Stilbestrol 1 mg. 3 times daily was initiated in January, 1956, but persistent back pain required narcotics for relief. In June, 1957, he was placed on 19-nor-ethinyl testosterone without relief. Cortisone acetate, 100 mg. each day, seemed to help for a short time. By December, 1958, his pain was so severe that he was admitted to the hospital for X-ray therapy to the thoracic spine. Relief was short-lasting. On this admission the pain was said to be very severe and to involve the neck, shoulders, entire back, and extremities. On examination tenderness could be elicited over the entire skeleton, and inguinal lymph nodes were large, indurated, and fixed bilaterally. Motor power was decreased in both arms and legs, and a sensory defect involving S_1, S_3, S_4 and S_5 was noted. On rectal examination the prostate was markedly enlarged, stony-hard, nodular, with extension into the seminal vesicles and laterally.

Investigations. Bone survey X-rays revealed massive sclerosis of the spine and pelvis. Serum phosphatases were: acid, 0.3 and alkaline, 9.9 Bodansky units. Hematocrit was 34.3 per cent; serum urea nitrogen, 13 mg. per cent. A radioiodine uptake study demonstrated euthyroidism. Urinary steroid values expressed in mg. per 24 hours were: crude neutral, 14.4; total ketonic, 8.8; alpha ketonic, 8.1; androsterone, 0.66; etiocholanolone, 1.68; androsterone/etiocholanolone ratio, 0.39; 11-ketoetiocholanolone, 0.50; 11-hydroxyandrosterone, 0.33; 11-hydroxyetiocholanolone, 0.39; and androgen/corticoid ratio, 1.92.

Treatment and course. On February 27, 1959, hypophysectomy via frontal craniotomy was performed under general anesthesia and hypothermia by Dr. David S. Rasmussen-Taxdal. The patient withstood the procedure well, and except for mild diabetes insipidus

and hypothyroidism had no complications during this admission. Prior to discharge, serum phosphatases were: acid, 1.1 and alkaline, 10.0 Bodansky units. Repeat urinary steroid values expressed in mg. per 24 hours were: crude neutral, 12.5; total ketonic, 3.1; alpha ketonic, 2.7; 11-hydroxyandrosterone, 0.15; 11-hydroxyetiocholanolone, 0.24; and androgen/corticoid ratio, 0.65.

Three months after hypophysectomy, the patient was almost free of pain and showed no neurologic deficit. Serum phosphatases were: acid, 0.9 and alkaline, 18.8 Bodansky units. The inguinal lymph nodes were smaller and softer. On rectal examination the prostate was felt to be small and soft, however, still fixed and nodular, with only minimal lateral extension. A differential blood count was normal. A radioiodine uptake study revealed mild hypothyroidism. He was continued on the following medications: cortisone acetate, 50 mg. a day; desiccated thyroid, 64 mg. a day; pituitary snuff, as necessary.

He continued to do well for several more months, but by October, 1959, some seven months after hypophysectomy, he began to have recurrent bone pain of severe degree. Combined with this, it became obvious on study that he was uremic secondary to lower ureteral obstruction by prostatic cancer. He was readmitted to this hospital on November 24, 1959, and died during the early morning of December 3, 1959, nine months postoperative. X-rays of the skeleton suggested some decrease in size and density of osseous metastases. Serum phosphatases two days before death were: acid, 0.2 and alkaline, 4.4 Bodansky units. On this day the serum urea nitrogen was 91 mg. per cent. Permission for autopsy was refused.

Clinical evaluation. In our opinion, this patient experienced subjective and objective benefit from hypophysectomy for about seven months.

CASE 12. H.H. This 68-year-old Negro male was readmitted to the Johns Hopkins Hospital on June 10, 1960, because of severe bone pain and urinary retention. In March, 1959, bilateral orchiectomy was performed and stilbestrol therapy initiated, at another hospital, because of advanced prostatic cancer. Response to these therapies was good and lasted about nine months. On admission here an inlying catheter was placed, and a transfusion was given for anemia. The prostate gland was felt to be moderately enlarged, nodular, hard, and fixed. Bilateral gynecomastia was present, and the lower extremities exhibited 1 + edema. On June 13, 1960: a transurethral resection was performed and a positive tissue diagnosis of adenocarcinoma of the prostate was made. This procedure was complicated by severe bleeding, although no hematological disorder could be demonstrated, and necessitated repeated transfusions, clot evacuations, cystotomies, packings, etc., but bleeding continued.

Investigations. X-rays of the skeleton revealed widespread osteoblastic and osteolytic lesions of the pelvis bones, thoracic and lumbar vertebrae, and upper femora. Serum phosphatases were: acid, 0.9 and alkaline, 37.9 Bodansky units. The serum urea nitrogen was normal (14 mg. per cent), as were serum electrolytes. The prothrombin time was 23 seconds or approximately normal. The platelet count and plasma fibrinogen level were normal. Total urinary 17-ketosteroids were 2.8 mg. per 24 hours.

Treatment and course. On July 11, 1960, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. Thomas W. Langfitt. The

patient withstood the operation well. Urethral bleeding ceased within a few days of operation. Pronounced diabetes insipidus occurred shortly after operation and has been controlled to the present with pituitary snuff. He continues to receive cortisone acetate, 12.5 mg. twice daily. At this writing the patient was last seen in the clinic on May 2, 1961, eleven months after hypophysectomy. He professed a good appetite, experienced no pain, had gained weight, and felt well generally. Many osteolytic lesions seen on the films made on June 13, 1960, one month before hypophysectomy, had undergone blastic changes by March 7, 1961. On rectal examination (Dr. Horst Schirmer) "no palpable prostate" was in evidence.

Clinical evaluation. In our opinion, this patient continues to experience subjective and objective benefit from hypophysectomy for a period now of over nine months.

CASE 13. G.P. This 75-year-old Negro male was admitted to the Johns Hopkins Hospital on July 26, 1960, with a history of moderately severe pain in his lower back and right hip of three months' duration, excruciating pain in his right hip, and inability to walk of three days' duration. X-rays revealed an intertrochanteric fracture of the right femur, the bone in this area being "moth-eaten" in appearance. Osteolytic areas were also seen in the right pubis, ischium, and ilium. On the day of admission, an open reduction and Ken nailing were performed. Tumor in the bone was encountered, and sections revealed "metastatic, osteolytic adenocarcinoma, consistent with a prostatic primary." Shortly after, the patient was transferred to the G.U. Service. On examination, the right hip and leg were in a cast. On rectal palpation, the prostate gland was markedly enlarged, nodular, stony-hard, fixed, and the process had extended into the right pelvis.

Investigations. Serum phosphatases were: acid, 0.5 and alkaline, 8.0 Bodansky units. Hematocrit was 33 per cent; serum urea nitrogen, 9 mg. per cent.

Treatment and course. On August 3, 1960, a transurethral resection was performed to relieve obstruction and to secure prostatic tissue for section. These sections revealed adenocarcinoma of the prostate. Bilateral orchiectomy was performed at the time of transurethral resection. On August 26, 1960, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. Thomas Langfitt. The immediate postoperative course was uneventful. However, healing of the nailed fracture was impaired by a mixed Gram-positive bacterial infection. The patient expired on October 27, 1960, from an overwhelming Gram-positive septicemia. Postoperative studies of thyroid function revealed a reduction in radioactive iodine consistent with mild hypothyroidism. Diabetes insipidus never occurred. An autopsy was not permitted.

Clinical evaluation. In our opinion, this patient did not survive hypophysectomy long enough to determine its effect. Death was due to a complication of nailing of a pathological fracture of the hip. Also, hypophysectomy was performed too soon after castration to permit one to determine its effect alone.

CASE 14. W.P. This 53-year-old Negro male was admitted to the Johns Hopkins Hospital on July 20, 1960, because of marked lower urinary tract obstructive symptoms of rather short duration. On rectal examination the prostate gland was slightly enlarged, nodular, hard, and fixed. Serum acid phosphatase was elevated, and metastases were present on X-ray. On July 22, 1960, transurethral resection was performed to relieve

obstruction and to secure tissue for diagnosis. Sections revealed diffuse adenocarcinoma of the prostate. On July 25, 1960, bilateral orchiectomy was performed.

Investigations. As indicated, X-rays revealed osteoblastic metastases in the neck of the left femur, in the body of the second lumbar vertebra, and in the skull. Serum phosphatases were: acid, 4.2 and alkaline, 4.2 Bodansky units. Hematocrit was 40 per cent, and serum urea nitrogen, 16 mg. per cent.

Treatment and course. On August 1, 1960, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. Thomas W. Langfitt. For the first time in our experience, a small amount of Zenker's solution was placed in the fossa. His postoperative course was quite uneventful, and he was discharged on the eighth postoperative day on 12.5 mg. cortisone acetate twice daily. Within ten more days he had returned to his work involving physical labor.

When seen in the clinic on January 24, 1961, he was voiding well and had developed no pain. His only complaint was mild polydipsia and polyuria, with a urinary specific gravity of 1.013. Serum phosphatases were: acid, 0.7 and alkaline, 4.8 Bodansky units. X-rays revealed no change in the appearance of osseous metastases when compared with films made on July 20, 1960.

His most recent clinic visit was on May 25, 1961, almost ten months after castration-hypophysectomy therapy. He was free of pain, voiding well, and working at hard labor. On rectal examination his prostate was smaller and softer.

Clinical evaluation. In our opinion, this patient has improved both subjectively and objectively following combined castration-hypophysectomy therapy. One cannot ascribe improvement to either procedure alone.

CASE 15. M.W. This 63-year-old Negro male was readmitted to the Johns Hopkins Hospital on December 20, 1960, for further treatment of widespread prostatic cancer. In October, 1958, he developed a staggering gait and symptoms of seventh nerve paralysis. At this time X-rays showed osseous metastases. Serum phosphatases were: acid, 1.2 and alkaline, 10.8 Bodansky units. Sections obtained by transurethral resection confirmed the clinical impression of prostatic carcinoma. In July, 1959, castration was performed because the patient had lost considerable weight. Response for three months was fair, but in October, 1959, stilbestrol therapy was initiated because of persistent elevation of serum phosphatases. By April, 1960, further deterioration was observed, and the primary growth continued to enlarge to this admission. On examination the patient appeared pale and chronically ill, with evidence of weight loss. Paralysis of the left seventh nerve was noted. Both legs and the right arm showed motor weakness but no sensory loss. The prostate gland was enlarged, stony-hard, nodular, and fixed.

Investigations. X-rays of the entire skeleton revealed metastatic, osteoblastic changes in all of the bones visualized except the skull. Serum phosphatases were: acid, 1.2 and alkaline, 23.6 Bodansky units. His admission hematocrit was 24 per cent, rising to 31 per cent after 2 units of blood. Serum urea nitrogen was 11 mg. per cent.

Treatment and course. On December 27, 1960, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. Gordon Long. The postoperative course was quite uneventful, and the patient was discharged from the hospital on January 13, 1961, on cortisone acetate, 50 mg. per day and pituitary snuff. Prior to discharge, his hematocrit had risen to 46 per cent. He was readmitted to this medical service on March 10, 1961, because of severe constipation, dehydration, low-grade fever, and mild hypotension. Examination revealed a fecal impaction which was removed. Fluid replacement therapy and an increase in the dosage of cortisone resulted in marked improvement. On March 20, serum phosphatases were: acid, 0.2 and alkaline, 20.5 Bodansky units. He was discharged again on March 27, 1961, only to be returned to the Accident Room on March 29, 1961, dead on arrival. An autopsy was not permitted.

Clinical evaluation. In our opinion, this patient was not benefited by hypophysectomy although his last serum phosphatase was normal. He survived the procedure three months and two days.

CASE 16. W.S. This 65-year-old Negro male was readmitted to the Johns Hopkins Hospital on October 31, 1960, for further treatment of widespread prostatic cancer. The case having been followed in this clinic since 1954 for urethral strictures, prostatic cancer was suspected on admission here February 24, 1960. This was confirmed by transurethral resection on February 26, 1960. X-rays at this time revealed no osseous metastases. Serum phosphatases were: acid, 0.7 and alkaline, 6.7 Bodansky units. On March 4, 1960, castration was performed. Shortly after the admission for hypophysectomy, he developed severe pain in his right upper arm and both legs. On examination a swelling was noted over the upper end of the right humerus. There was pain and limitation of motion of the left leg. The prostate gland was large, hard, and fixed.

Investigations. X-rays of the skeleton revealed a possible lytic lesion in the right humerus. Serum phosphatases were: acid, 1.4 and alkaline, 15.3 Bodansky units. His serum urea nitrogen ranged from 14 to 80 mg. per cent, secondary to bilateral hydronephrosis demonstrated on intravenous pyelogram. On November 3, 1960, an open biopsy of the right humerus was performed and revealed a metastasis from his prostatic cancer.

Treatment and course. On November 17, 1960, hypophysectomy was performed via right frontal craniotomy under general anesthesia without hypothermia by Dr. Thomas W. Langfitt. The postoperative course was quite uneventful, and the patient was discharged on November 28, 1960. When seen in the clinic on December 8, 1960, he felt well and his serum phosphatases were: acid, 0.9 and alkaline, 31.4 Bodansky units. When last seen by us on February 14, 1961, he was free of pain and felt well generally. Blood chemistries were not drawn and no X-rays were taken. We have learned that this patient died at another Baltimore hospital on March 7, 1961, almost six months after hypophysectomy.

Clinical evaluation. In our opinion, this patient experienced some subjective benefit. He showed an objective improvement in renal function possibly secondary to a lessening of lower ureteral obstruction as a result of shrinkage of the local cancer extension.

CASE 17. J.S. This 68-year-old white male was readmitted to the Johns Hopkins Hospital on January 5, 1961, for further treatment of widespread prostatic cancer and right hydroureteronephrosis, secondary to obstruction of the right ureterovesical junction by prostatic cancer. His first admission here was on November 27, 1959, at which time he experienced marked symptoms of lower urinary tract obstruction. Eighteen months

prior to this first admission, his local physician had made a diagnosis of prostatic cancer, based on rectal findings, and had performed castration and initiated estrogen therapy. On this admission serum phosphatases were: acid, 0.7 and alkaline, 11.1 Bodansky units. X-rays had revealed questionable metastases to the right ilium and sacrum. On December 2, 1959, a transurethral resection was performed, and sections of the prostate revealed diffuse, poorly differentiated adenocarcinoma. At this time both ureteral orifices could not be seen, presumably because of subtrigonal prostatic cancer. The right renal collecting system could not be seen on a 1-hour postinjection film. He was discharged on December 6, 1959, on stilbestrol, 1 mg. three times daily. He was readmitted in August, 1960, for a second transurethral resection for obstruction. Serum phosphatases were: acid, 0.4 and alkaline, 3.2 Bodansky units. On this admission (January 5, 1961) a left nephrostomy was performed on January 9, 1961, to insure drainage of this kidney which was now involved in hydronephrosis and was the only functioning kidney. His chief complaints now were severe midepigastric pain, associated with nausea, vomiting, and constipation.

Investigations. X-rays of the skeleton again revealed questionable metastases to the right ilium and sacrum. Serum phosphatases were: acid, 1.4 and alkaline, 3.1 Bodansky units. An initial hematocrit was 28 per cent and was raised by transfusions. The serum urea nitrogen was 30 mg. per cent.

Treatment and course. On January 17, 1961, hypophysectomy was performed via frontal craniotomy under general anesthesia and hypothermia by Dr. Thomas W. Langfitt. His immediate postoperative course was fair, but complicated by a rising serum urea nitrogen and the necessity of replacing the left nephrostomy tube on several occasions. However, on the tenth postoperative day he began to do poorly, and by January 31, he was vomiting blood. A surgical consultant suspected a perforating duodenal ulcer, which was found at laparotomy on February 5, 1961. A Billroth II anticolic Polya gastrectomy was performed. This procedure was complicated by pneumonia and the necessity of replacing his left nephrostomy tube on two occasions. However, by February 16, 1961, he looked and felt well, his electrolytes were within normal ranges, his hematocrit was 42 per cent, and his serum urea nitrogen was 23 mg. per cent. He was discharged on February 19, 1961, on cortisone acetate, 12.5 mg. twice daily, in combination with pituitary snuff. He was last seen in this clinic on February 28, 1961. His pain was less severe, requiring only salicylates, and he had gained strength and weight. The only chemistry drawn at this visit was a serum urea nitrogen reported to be 16 mg. per cent.

Clinical evaluation. In our opinion, the short follow-up period precludes an evaluation of the effect of hypophysectomy.

RESULTS

Under the heading, "Methods and Materials," we have already stated how difficult we think it is to evaluate a procedure which is palliative and not curative. Therefore, results will be expressed according to somewhat arbitrary criteria, without serious pronouncement of the value of each.

The effect of hypophysectomy on survival. Since many factors contribute to "survival-times," to suggest at this time that hypophysectomy increased

the life-span of any of the seventeen patients studied would be fallacious. For example: (*a*) there is increasing evidence that the histological grade of the tumor is the most important single factor in determining prognosis, almost irrespective of the type of therapy employed (8); (*b*) length of survival is somewhat dependent upon when treatment is begun in the course of the disease. In this regard, the co-operative study described by Nesbit and Baum (9) clearly indicated that those patients with prostatic cancer who had metastases at the time when castration-estrogen therapy

TABLE 1

LENGTH OF SURVIVAL FOLLOWING CASTRATION AND HYPOPHYSECTOMY

Case Number	Date of Onset of Symptoms	Date of Diagnosis	Date of Castration	Date of Hypophysectomy	Date of Death	Length of Survival	
						Posthypophysectomy	Postcastration and Hypophysectomy
1. J. K.	8/45	8/11/48 (T*)	.....	9/24/48	10/4/48	11 days	.....
2. G. W.	8/51	10/10/51 (C**)	.....	11/16/51	4/26/52	5.5 months	.....
3. B. S.	2/49	2/19/52 (C**)	9/10/50	3/11/52	4/14/52	34 days	1 year, 7 months
4. J. B.	2/50	12/19/51 (T*)	12/19/51	4/1/52	1/11/53	9 months, 11 days	13 months
5. N. K.	10/49	10/7/49 (T*)	9/7/51	10/24/52	10/26/52	2 days	14 months
6. W. B.	10/50	12/7/50 (C**)	6/8/51	11/4/52	11/27/53	1 year, 23 days	2 years, 7 months
7. J. H.	9/56	1/10/57 (T*)	8/12/57	11/3/58	8/20/60	1 year, 10 months	3 years
8. A. F.	8/53	11/29/54 (T*)	11/29/54	12/2/58	12/8/58	7 days	4 years, 9 days
9. L. F.	1/56	11/28/56 (C**) 10/6/58 (T*)	11/28/56	1/9/59	12/30/59	12 months	3 years, 1 month
10. E. L.	4/58	11/28/58 (C**)	12/1/58	2/16/59	4/11/59	3 months	4 months
11. F. J.	2/55	11/23/55 (T*)	11/23/55	2/27/59	12/3/59	9 months	4 years
12. H. H.	1/59	3/59 (C**) 6/13/60 (T*)	3/59	7/11/60	Alive+	11 months	2 years, 2 months
13. G. P.	5/60	7/26/60 (T*)	8/3/60	8/26/60	10/27/60	2 months	3 months
14. W. P.	7/60	7/22/60 (T*)	7/25/60	8/1/60	Alive+	10 months	10 months
15. M. W.	10/58	10/16/58 (T*)	7/27/59	12/27/60	3/29/61	3 months	1 year, 8 months
16. W. S.	2/60	2/26/60 (T*)	3/4/60	11/17/60	3/7/61	4 months	1 year
17. J. S.	3/58	3/58 (C**) 12/2/59 (T*)	3/58	1/17/61	Alive+	5 months	3 years, 2 months

* T indicates the date of a positive tissue diagnosis.

** C indicates the date of a positive clinical diagnosis evidenced by elevated serum acid phosphatase and osseous metastases.

\+ Indicates that the patient was alive as of June 1, 1961.

was initiated did not live as long on the average as those without demonstrable metastases; (*c*) the influence of previous endocrine therapy, such as castration, on subsequent endocrine therapy, such as hypophysectomy, has not been assessed. In this regard, many workers in the field have the impression that the majority of responders to one form of hormonal therapy will respond to a second form of hormonal therapy administered later.

There were three deaths in this series of seventeen patients which we attributed to the operation, or an operative mortality of 18 per cent. In ten of the remaining fourteen, the postoperative course was judged to be benign.

Table 1 shows the length of survival in all patients in this series, both

after castration and after hypophysectomy, together with the date of the onset of symptoms and the date of the diagnosis. Three patients are living at this writing, one of whom (Case 14) underwent hypophysectomy shortly after castration. Eleven patients who were castrated suffered relapse and were subsequently hypophysectomized. They lived an average of *25.6 months* from the time of castration. Ten patients subjected to hypophysectomy in the treatment of relapse following castration (and usually estrogen) therapy lived an average of *8 months* after hypophysectomy. This figure excludes the three postoperative deaths (Cases 1, 5, and 8), one patient

TABLE 2

COMPARISON OF RESPONSE FOLLOWING CASTRATION TO RESPONSE FOLLOWING SUBSEQUENT HYPOPHYSECTOMY

Case Number	Pretreatment Progression	Response to Castration		Response to Subsequent Hypophysectomy	
		Subjective	Objective	Subjective	Objective
3. B. S.	Moderately fast	+	0	0	0
4. J. B.	Fast	0	0	0	0
6. W. B.	Fast	+	+	+	+
7. J. H.	Fast (Pain)	+	0	+	+
9. L. F.	Slow	+	+	+	+
10. E. L.	Fast	0	0	+	+
11. F. J.	Fast	0	0	+	+
12. H. H.	Fast	+	+	+	+
15. M. W.	Slow	+	+	0	0
16. W. S.	Slow	0	0	+	+

subjected to hypophysectomy only (Case 2), two patients who are living (Cases 12 and 17), and one patient who is living but whose hypophysectomy followed castration within one week (Case 14).

It seems unnecessary to carry this analysis of "survival-times" further. Undoubtedly "survival-times" following castration therapy were either shortened or lengthened in certain instances by subsequent hypophysectomy.

Subjective and objective response to hypophysectomy. Table 2 was prepared to show a comparison between our clinical and laboratory evaluation of the response in each patient following castration to that following subsequent hypophysectomy. An estimate of the rate of progression of the disease prior to any hormonal therapy is also shown. In this comparison, a

positive *subjective* response is recorded if any *one* of the following changes was observed: relief of pain; improvement in appetite and sense of well-being; gain in weight. A positive *objective* response is recorded if any *one* of the following was observed: a lowering of serum acid phosphatase activity to normal; a decrease in the size of the primary lesion; a disappearance of a neurologic deficit; an improvement in the X-ray appearance of osseous metastases. Cases 1 and 2 were excluded from this comparison because hypophysectomy was the sole treatment; Cases 13 and 14 because hypophysectomy was performed only a short time after castration; Cases 5 and 8 because both died as the result of hypophysectomy; and Case 17 because of too short a follow-up after hypophysectomy.

Both procedures failed to provide subjective or objective improvement in one patient (Case 4); a good response followed both procedures in four patients (Cases 6, 7, 9, and 12); two patients were not benefited by hypophysectomy but were benefited by castration (Cases 3 and 15); and three patients responded to hypophysectomy after castration had failed to provide subjective or objective improvement (Cases 10, 11, and 16). However, it must be noted that these last three patients survived hypophysectomy for only three, nine, and four months, respectively, and in two of them (Cases 11 and 16) the interval between castration and hypophysectomy was longer than the interval between hypophysectomy and death.

To us, these comparisons are probably meaningless. Again they point out our lack of reliable criteria on which to base an evaluation as well as the fact that the degree of palliation depends to a great extent on when in the course of the disease any hormonal therapy is instituted.

Lastly, judging the degree of palliation on the basis of clinical impression *alone*, without regard to measurements of the size of the local lesion, the level of serum acid phosphatase activity, or the appearance of osseous metastases on X-ray, we believe that four patients experienced genuine benefit from hypophysectomy (Cases 6, 7, 12, and 14). The first three were in relapse following castration-estrogen therapy, and the last underwent hypophysectomy too soon after castration to permit one to judge its effect. It is of interest that these four patients responded well to castration.

The effect of hypophysectomy on serum acid phosphatase. Multiple determinations of serum acid phosphatase activity were made in eleven of the seventeen patients in this series (Table 3), all of whom had elevated values

prior to hypophysectomy. Following hypophysectomy, these levels fell to normal in six; in five they remained elevated. In the remaining six of the seventeen, only preoperative values are available.

If one can make any deduction from these observations, it would be that those patients whose serum acid phosphatases returned to normal lived somewhat longer than would have been the case if this activity had remained elevated. (Compare "survival-times" of Cases 7, 9, 11, 12, 14, and 16, whose serum acid phosphatases returned to normal after hypophysectomy, with "survival-times" of Cases 2, 4, 6, 15, and 17, in whom serum acid phosphatases remained elevated.)

TABLE 3

SERUM ACID PHOSPHATASE ACTIVITY BEFORE AND AFTER HYPOPHYSECTOMY

Case Number	Before Hypophysectomy	After Hypophysectomy	Length of Survival after Hypophysectomy
1. J. K.	Elevated	No determination	11 days
2. G. W.	Elevated	Elevated	5.5 months
3. B. S.	Elevated	No determination	34 days
4. J. B.	Elevated	Elevated	9 months, 11 days
5. N. K.	Normal	No determination	2 days
6. W. B.	Elevated	Elevated	1 year, 23 days
7. J. H.	Elevated	Normal	1 year, 10 months
8. A. F.	Elevated	No determination	7 days
9. L. F.	Elevated	Normal	12 months
10. E. L.	No determination	No determination	3 months
11. F. J.	Elevated	Normal	9 months
12. H. H.	Elevated	Normal	Alive, 11 months
13. G. P.	Elevated	No determination	2 months
14. W. P.	Elevated	Normal	Alive, 10 months
15. M. W.	Elevated	Elevated	3 months
16. W. S.	Elevated	Normal	4 months
17. J. S.	Elevated	Elevated	Alive, 5 months

The effect of hypophysectomy on the X-ray appearance of osseous metastases. We have found it difficult in most instances to interpret changes in the X-ray appearance of metastases following hormonal therapy as to whether or not such changes represent improvement or progression. Our impression is that the most significant changes occur after castration, and that an osteoblastic response followed by an apparent disappearance of osseous metastases represents improvement, even though at a later date metastases reappear on X-ray of the same areas. We have never been able to observe such changes after bilateral adrenalectomy.

Only three patients in this series of seventeen showed changes in the X-ray appearance of their osseous metastases after hypophysectomy. We

interpreted this as representing improvement; the rest we judged to show progression. Nine months after hypophysectomy, Case 6 showed a decrease in density and extent of metastases. Case 7, seven months after hypophysectomy, showed an osteoblastic response of his predominantly lytic metastases. Case 10, nine months after operation, showed some decrease in the size and density of a number of metastases.

The effect of hypophysectomy on urinary 17-ketosteroids. Determinations of urinary 17-ketosteroids were made in eight of the seventeen patients in this series both before (1 week) and after (4–5 weeks) hypophysectomy. In four, values are available for so-called "total urinary 17-ketosteroids";

TABLE 4

URINARY 11-DESOXY- AND 11-OXY-17-KETOSTEROIDS BEFORE AND AFTER HYPOPHYSECTOMY*

Case Number	Relation to Operation	Crude Neutral	Total Ketonic	Alpha Ketonic	Androsterone	Etiocholanolone	Androsterone/Etiocholanolone Ratio	11-Ketoetiocholanolone	11-Hydroxyandrosterone	11-Hydroxyetiocholanolone	"Androgenic"/Corticoid Ratio
7. J. H.	Before	8.4	4.8	2.1	0.32	0.51	0.63	0.25	0.13	0.15	1.56
	After	8.2	1.9	1.5 (−28%)	0.17 (−47%)	0.34 (−33%)	0.50	0.43 (+72%)	<0.05	0.18 (−20%)	0.84
9. L. F.	Before	6.8	6.2	5.4	1.12	1.63	0.69	0.40	0.16	0.36	2.99
	After	11.5	4.5	3.7 (−31%)	0.46 (−59%)	0.72 (−56%)	0.64	0.62 (+55%)	<0.05	0.20 (−44%)	0.80
10. E. L.	Before	4.8	1.7	1.3	0.27	0.22	1.23	0.20	0.10	0.12	1.16
	After	10.8	1.7	1.0 (−23%)	0.18 (−33%)	0.20 (−10%)	0.90	0.12 (−40%)	<0.05	<0.05	3.16
11. F. J.	Before	14.4	8.8	8.1	0.66	1.68	0.39	0.50	0.33	0.39	1.92
	After	12.5	3.1	2.7 (−66%)	0.18 (−73%)	0.54 (−68%)	0.33	0.71 (+42%)	0.15 (−54%)	0.24 (−38%)	0.65

* All values expressed in milligrams per 24 hours.
<0.05 = undeterminable.

in four, values are available for the two so-called "androgen" metabolites, androsterone and etiocholanolone, and for three "corticoid" metabolites, 11-hydroxyandrosterone, 11-hydroxyetiocholanolone, and 11-ketoetiocholanolone (Table 4). The methods of Dobriner and Gallagher (10, 11, 12) were used in determining the latter. These involve β-glucuronidase hydrolysis at pH 4.7; continuous ether extraction at pH 1.0; separation into crude acidic, neutral, and phenolic fractions; separation of the crude neutral fraction into α- and β-ketonic fractions with Girard's reagent; fractionation of the α-ketonic by chromatography on a silica gel column; identification of the five steroids described above by infrared spectrophotometry and final quantitation of these according to the Zimmerman reaction.

In the four patients for whom only total 17-ketosteroids are available, two showed a decrease after hypophysectomy, and two showed a slight to moderate increase. However, when careful separations were made in four patients, all four showed a decrease in both androsterone and etiocholanolone as shown in Table 4. Such values are more meaningful than values for total 17-ketosteroids and suggest that hypophysectomy resulted in less production of the adrenal precursors of androsterone and etiocholanolone.

STUDIES DONE TO DETERMINE THE COMPLETENESS OF HYPOPHYSECTOMY

As outlined above under "Methods and Materials," certain clinical determinations were made in a number of patients in an effort to assess the completeness of hypophysectomy.

Thyroid function. Radioactive iodine uptake studies were made in five patients (Cases 2, 6, 7, 11, and 13). In all, the slope indicated a hypothyroid state after hypophysectomy. In a number of others in which such studies were not made, clinical myxedema was evident and necessitated treatment with desiccated thyroid.

Pearson and Ray (13), in their careful study of 343 women subjected to hypophysectomy for carcinoma of the breast, found thyroid function depressed in the vast majority. However, they encountered ten patients with persistent thyroid function after complete or nearly complete hypophysectomy, which suggested that "the measurements of thyroid function are a useful but not infallible guide to the completeness of hypophysectomy."

Adrenal function. According to others (4), if cortisone substitution therapy is withheld, the completely hypophysectomized patient will develop adrenal insufficiency or crisis within two to seven days, but will not if hypophysectomy is incomplete. We believe that such a provocative test is not justified. However, several of our patients did develop acute adrenal insufficiency secondary to the stress of infection and required additional cortisone.

As indicated above (Table 4), hypophysectomy was followed in each instance by a reduction in urinary androsterone and etiocholanolone. In the absence of the testes, both of these metabolites are considered to be derived from an adrenal precursor, probably dehydroisoandrosterone. We interpret such data as evidence of interference with pituitary function. More data are necessary, but such measurements may prove to be useful in determining completeness of hypophysectomy.

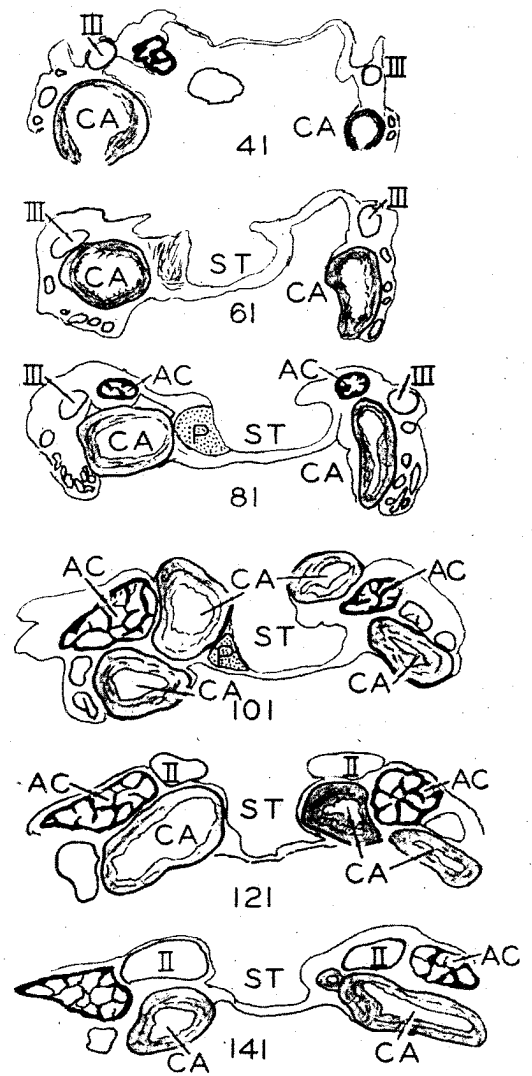

PLATE 1.—Representative serial sections to show the remaining pituitary tissue in Case 6.—W.B. The stippled area labeled "*P*" represents the pituitary nodule left. The abbreviations are as follows: *AC*, anterior clinoid process; *CA*, internal carotid artery; *ST*, sella turcica; *II*, optic nerve; *III*, oculomotor nerve.

Carbohydrate metabolism. Glucose tolerance tests were made in three patients before and after hypophysectomy (Cases 1, 2, and 6). Increased tolerances were observed in all, indicating pituitary insufficiency. In one of the three (Case 6), a decreased tolerance occurred prior to hypophysectomy and became normal after operation.

Fluid intake and output. No evidence of diabetes insipidus was observed in five of the seventeen patients in this series; mild, moderate, or severe diabetes insipidus was observed in twelve. However, we appreciate that the development of diabetes insipidus is not dependent upon the presence or absence of the anterior lobe of the pituitary and hence is of no real value in determining the completeness of hypophysectomy. As Bronson Ray has shown (14), diabetes insipidus is only transitory after hypophysectomy, especially if damage to the pituitary stalk is minimal. When it persists, degeneration of the supra-optic and paraventricular nuclei is found at autopsy. He therefore recommends that the pituitary stalk be divided close to the pituitary when removing it.

Testicular function. Two patients (Cases 1 and 2) were subjected to hypophysectomy only. One patient (Case 2) lived five and one-half months and died of a pulmonary embolus. At autopsy, testicular atrophy was present. Atrophy of the testes was not evident in the other patient (Case 1), who died on the eleventh postoperative day. In this regard, Pearson *et al.* (4) observed "testicular atrophy" in two males within a few weeks after hypophysectomy.

Anatomic studies. Autopsies were performed on seven of the fourteen patients, and serial sections of the sella turcica were made on four. In no instance was hypophysectomy complete. Estimations of the amount of residual pituitary tissue were as follows: Case 2, 12 per cent; Case 3, 30–35 per cent; Case 4, 35–50 per cent; Case 6, 5 per cent. Plate 1 shows the representative serial sections in Case 6, in whom hypophysectomy was nearly complete.

On the basis of clinical observations and laboratory data, we predicted before autopsy that in two of these four patients hypophysectomy was probably complete or nearly complete, and such was found; in the remaining two we predicted that hypophysectomy was grossly incomplete, and this proved to be so. Interestingly enough, both patients whose hypophysectomies were nearly complete were judged to have been markedly benefited by the procedure, and neither died as a direct result of prostatic cancer.

DISCUSSION

Twenty years ago Charles Huggins (15) first demonstrated the marked beneficial response of patients with disseminated prostatic cancer to castration and estrogen therapy. This response has since become thoroughly established. Today there seems to be no doubt that these are still the best forms of hormonal therapy.

The mechanisms by which castration and estrogen therapy exert their favorable actions are not entirely clear, but there is a growing body of evidence to support Huggins' original contentions that androgens stimulate growth of prostatic cancer and that elimination of testicular androgens by castration, or "neutralization" of androgens by estrogen administration, will frequently retard the growth of this cancer. Most conclusive evidence in support of Huggins' views is given by the studies of Burt *et al.* (16) on the steroid response to therapy in prostatic cancer. The interested reader is referred to this article for details. A verbatim summary of this work follows:

"Androgen" metabolites fall after castration.

"Corticoid" and "androgen" metabolites may rise when a patient relapses.

Gonadotrophin has no effect on steroid levels in the castrate patient.

The effect of ACTH on both "androgen" and "corticoid" metabolites is markedly enhanced by castration.

Stilbestrol causes a fall in "androgen" and "corticoid" metabolites in the intact and castrate patient.

Cortisone can effectively eliminate "androgen" metabolites.

The tendency to relapse from therapy may be associated with the degree of conversion of certain precursors, such as testosterone, to androgenic androsterone rather than physiologically inactive etiocholanolone.

In our limited series, the clinical state has invariably paralleled the chemical state.

We appreciate that androgen excretion does not necessarily measure androgen production, but we contend that it frequently approximates it and that until one can measure blood androgens accurately and feasibly, one must depend upon urinary levels.

Thus it seems to us that one logical approach to therapy for the patient with prostatic cancer who has relapsed on castration-estrogen therapy is to search for means of suppressing or eliminating an extragonadal source of androgen. This idea is not new; it represented the basis for the introduction of bilateral adrenalectomy by Huggins and one of us (17).

Whereas Huggins and his associates (18, 19), as well as others (20), have

demonstrated that bilateral adrenalectomy results in both subjective and objective improvement in a large number of women with disseminated breast cancer, there are no comparable reports to permit accurate evaluation of this procedure in the treatment of prostatic cancer. However, it has been demonstrated that bilateral adrenalectomy has been of benefit in some (21, 22), and we believe that a more extensive trial should be conducted.

Hypophysectomy is another approach which has been based on similar considerations. A word or two about the rationale for hypophysectomy: (*a*) it is believed that hypophysectomy abolishes the production of androgen by the testes by removing the source of the pituitary hormone which stimulates the Leydig cells (ICSH); (*b*) in like manner it is believed that by removing the source of ACTH, androgen production by the adrenal is reduced or abolished; (*c*) there is evidence to suggest that two other trophic hormones of the pituitary, prolactin (23) and somatotrophin (24), synergize the action of testosterone; (*d*) evidence is accumulating which indicates that the pituitary, through its growth hormone, may be concerned with neoplastic growth (25, 26, 27, 28) and that hypophysectomy will inhibit certain forms of tumors induced chemically (29).

It is not the purpose of this paper to present an exhaustive review of all published cases in which hypophysectomy has been performed in the treatment of prostatic cancer or to compare hypophysectomy with bilateral adrenalectomy in the treatment of this cancer. Actually, a scarcity of published reports in which either procedure has been done prevents such comparison. However, a few reports will be considered.

In 1957, Luft and Olivecrona (30) reviewed their results in seventy-five patients in whom hypophysectomy had been performed in the treatment of malignant tumors. Ten were done for prostatic cancer, the first on May 9, 1952. There were three postoperative deaths, and remissions were obtained in five of the remaining seven patients. Remissions were brief in two, namely two and three months, and ranged from eight to twenty-four months in three. At the time of their report, one patient who had failed to respond to stilbestrol therapy was alive and well twenty-four months after hypophysectomy.

Heretofore the largest published series of hypophysectomies for prostatic cancer is that of Bronson Ray (31): "Of 16 patients with prostatic cancer all had far advanced disease and had already received most of the

forms of treatment commonly employed, yet six of the number were benefited by hypophysectomy." Unfortunately, no other data were published regarding these patients except for reference to one in an earlier report in 1956 (4): "Of four patients with prostatic cancer whose disease was in relapse after orchiectomy and estrogen therapy, one obtained an objective remission from hypophysectomy. The remission lasted for 15 months, followed by relapse. In this patient there was a prompt fall in acid phosphatase to normal levels after hypophysectomy and there was regression in the size of the primary lesion." This patient also showed some improvement of a neurological deficit.

Finally, regarding published reports, Smith *et al.* (5), in 1959, reviewed their results in five patients with advanced prostatic cancer who had undergone surgical hypophysectomy. "All four who survived the operation have shown worthwhile subjective and objective improvement which in two patients has so far lasted over one year. Three of these patients had relapsed after responding to estrogen treatment (only), but subsequently improved after hypophysectomy."

We wish to conclude this discussion with a brief résumé of what we think we have learned from our study, as well as from those of others.

Transfrontal hypophysectomy is a procedure which can be performed without great risk, and postoperative management is not difficult. We have never succeeded in performing complete hypophysectomy, although three of our patients are alive and an anatomic determination of completeness of removal has not been possible. However, Bronson Ray (13), who has had a tremendous experience with hypophysectomy for breast cancer in women, has demonstrated by serial sections of the sella turcica that hypophysectomy has been complete in twenty-one of thirty-five of his patients. As yet it is not possible to determine whether functionally complete hypophysectomy requires complete anatomical removal, but it does appear as if complete or nearly complete removal can be predicted by functional tests and that better results are obtained when most or all of the pituitary is removed. As noted by us and others (13), the patient who has undergone hypophysectomy can lead a normal life, possessing a normal appearance and normal mental and physical functions.

There is no doubt that hypophysectomy will benefit some patients after they have relapsed following castration-estrogen therapy. However, the

frequency of a good response has not been determined on a large scale; nor is comparison now possible with bilateral adrenalectomy.

Indications for hypophysectomy are not clear as yet. We believe that there is little justification for performing hypophysectomy as a primary procedure and rely on castration-estrogen therapy initially. We have the impression that a good response to castration-estrogen therapy will usually be followed by a good response to hypophysectomy when performed in the treatment of relapse. However, failure to respond to castration-estrogen therapy does not preclude a response to hypophysectomy. Based on our studies of urinary steroids (16), we believe that hypophysectomy is indicated in the patient in relapse following castration-estrogen therapy whose urinary "androgenic" steroids remain elevated or continue to rise in spite of cortisone therapy.

There is much more to be learned not only about the effectiveness of hypophysectomy in the treatment of prostatic cancer but about bilateral adrenalectomy as well. We know of no way of determining effectiveness short of increasing our experience by doing more. As secondary therapies to oöphorectomy, both bilateral adrenalectomy and hypophysectomy have proved to be of real value in the treatment of breast cancer, and it is possible that a similar response would be found if more patients with disseminated prostatic cancer in relapse after castration-estrogen therapy were subjected to hypophysectomy or adrenalectomy.

SUMMARY

The results of hypophysectomy in seventeen patients with disseminated prostatic cancer are presented. These results indicate that hypophysectomy may prove to be a worthwhile therapeutic procedure in the treatment of these patients who are in relapse following castration-estrogen therapy.

Certain factors which may influence the response to hypophysectomy are discussed. Two indices for predicting a favorable response to hypophysectomy are: a previous favorable response to castration-estrogen therapy and evidence of continued androgen production in such patients.

Hypophysectomy is recommended in the treatment of metastatic prostatic cancer in the patient who is in relapse following castration-estrogen therapy and in whom urinary "androgenic" steroids remain elevated in spite of cortisone administration.

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ALEXANDER LIPSCHUTZ

NERVOUS STIMULI AND TUMORIGENESIS

I have to apologize for my audacity in writing about the problem of whether nervous stimuli are involved in the genesis and evolution of tumors. I have not done any *work* in this field. And I am always aware of the great truth of Francis Bacon's words: that Man being but a servant and interpreter of Nature can "achieve" or be successful in interfering in Nature and understanding her, but "*Opere* vel Mente," that is, through "*Work* and Reflexion."[1] Some years later, Gracian, who also was a wise man, wrote: "*Turn the hand first to achievement and then to the pen.*"[2] All the more do I feel embarrassed by these truths when turning to the pen without previous achievement of my own, in a volume dedicated to our dear friend Charles Huggins, who never turned to the pen before having "achieved" *Opere* vel Mente.

However, I may argue that much work has been reported in recent years by various authorities on the influence of nervous stimuli on tumori-

ALEXANDER LIPSCHUTZ is academic member of the Faculty of Medicine of the University of Santiago, Chile, and was formerly professor of physiology and director of the Institute of Experimental Medicine of the National Health Service, Santiago, Chile.

[1] *Instauratio Magna: Distributio Operis* (1620): "Homo enim Naturae minister et interpres tantum facit et intelligit, quantum de Naturae ordine Opere, vel Mente, observaverit: nec amplius scit aut potest." Quoted from Francis Bacon, *Novum Organum Scientiarum*, 2d ed. (Amsterdam, 1660), p. 18.

[2] Lorenzo Gracian, *Oraculo Manual, y Arte de Prudencia* (Madrid, 1653). Quoted from the English edition: Baltasar Gracian, *A Truthtelling Manual and Art of Worldly Wisdom* (Springfield, Ill.: Charles C Thomas, 1939), p. 47.