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and
Minnesota Medical Foundation



Total Hypophysectomy

BULLETIN OF THE
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I. TOTAL HYPOPHYSECTOMY IN ADVANCED BREAST CANCER*

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Induced alterations in the hormonal balance of patients with advanced breast cancer have significantly modified in a favorable direction the anticipated behavior of the tumor. These alterations have been attained by the administration of sex steroid hormones or by deprivation of hormones producing tissues. Recently, total surgical hypophysectomy has been employed in a further attempt to produce favorable regression of tumor masses in advanced breast cancer.

Hormonal Factors in Breast Cancer

It has been long established in animal experiments and clinical observations that the administration or deprivation of certain hormones has modified the growth of breast cancer in the direction of either temporary regression or acceleration of the disease. Discrepancies have arisen because of the lack of correlation between some animal experiments and human observations. The demonstration that estrogenic hormones stimulate the development of mammary breast cancer in mice discouraged the use of these same hormones in selected human patients with advanced cancer; whereas, actually estrogenic hormones do produce favorable regressions in breast cancer in the postmenopausal woman. To consider the established hormonal factors in the growth

of human breast cancer, women are divided into two groups: the premenopausal woman and the postmenopausal woman.

A. The premenopausal woman: Premenopausal refers to those women with active menstrual cycles or established ovarian function. It includes the woman whose periods have ceased as the menopausal age is reached, but in whom there is cyclic ovarian activity as established by estrogen assay methods. It has long been recognized that in young women with osseous metastases from breast cancer, exacerbation of pain occurs prior to the menstrual period. This is associated with increased excretion of calcium in the urine and occasionally hypercalcemia due to rapid bone breakdown. On cessation of the menstrual period the pain subsides. This has been objectively demonstrated by metabolic observations and establishes the fact that certain carcinomas of the breast are dependent upon estrogenic hormones for maintenance of the growth rate.^{1,2} Furthermore, the administration of physiologic doses of estrogenic hormone in the presence of active ovarian function may sometimes accelerate the growth of breast cancer in the young woman.² However, only rarely has there been observed an intensified growth of breast cancer in premenopausal women with massive doses of estrogenic hormone (1000 mg. of stilbesterol per day), which invariably produces amenorrhea. In fact, with these large dose levels, regression of the tumor in a few patients has been noted. These findings suggest that inhibition of pituitary growth or tropic factors may play a role. It is also apparent that in such patients a large dose of estrogenic hormone in itself is not a stimulus to the tumor growth, and that other factors which have been suppressed by the large doses of estrogen are more important in stimulating or maintaining cancer growth than estrogen administration alone.

The occurrence of carcinoma of the breast during pregnancy is associated with a grave prognosis and the five-year survival rate of such women is low.

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From the Metabolic Research Unit of the Department of Medicine.

It has been suggested that the apparent acceleration of breast cancer during pregnancy is due to increased vascularity of the breast and hence ease of metastases, the presence of an increased amount of estrogenic hormone or other stimulating hormones, or unknown factors. The hormonal imbalance that occurs during this stage of a woman's life is such that women with previous breast cancers are urged not to become pregnant.

Androgenic hormones have been widely employed in the treatment of advanced breast cancer; however, with their use, an incidence of hypercalcemia in 10% of patients with osseous metastases has been observed. This "induced hypercalcemic syndrome" has been postulated to be due to an acceleration of tumor growth, resulting in more rapid destruction of bones thus flooding of the blood stream with calcium.³ It has not been established that this acceleration is due to a direct effect of the androgenic hormone on the tumor itself. More recently, steroid excretion patterns have been observed in patients with breast cancer receiving hormonal therapy.^{4,5} Estrone, estriol and estrodial have all been demonstrated to be excreted in significantly increased amounts during the administration of testosterone. It is now apparent that the androgenic hormone is converted, in part, to estrogen. This estrogenic hormone may be the factor that accounts for the stimulation and acceleration of tumor growth during the administration of androgenic hormone.

The demonstration that certain breast cancers in women are dependent upon estrogenic hormone for growth provides a physiologic basis for treatment of advanced cancer. Castration (radiation or surgical oophorectomy) removes a major source of estrogen. Remissions are regularly obtained in up to 50% of the women so treated. The removal of the estrogenic factor of the ovaries and/or the removal of other unknown ovarian factors eradicates the stimulus to tumor growth, but eventually in those patients who respond, a relapse occurs. In the castrated woman it has been observed that the pituitary and adrenal glands hypertrophy.

This hypertrophy appears to play an important role in the exacerbation of the disease.

The adrenal glands are a source of estrogenic and androgenic hormones and with the hypertrophy that appears following castration it might be that an increased production of these hormones occurs. Furthermore, other adrenal factors may exist that have stimulating or growth maintaining effect on tumor growth. The control of the adrenal gland is maintained largely by the pituitary adrenocorticotrophic hormone.

The pituitary gland (hypophysis) has an apparent increasing important role in the understanding of the growth mechanisms of breast cancer. The gonadotropic hormones directly control ovarian function and the production of ovarian hormones. Similarly, ACTH provides a stimulus to the adrenal cortex in an attempt to produce more steroid hormones. Perhaps most important is production of somatotrophic hormone (growth hormone) by the anterior lobe of the pituitary gland.

Animal experiments demonstrated that hypophysectomy in rats definitely retarded the growth of tumors from the day of the extirpation of the hypophysis.⁶ Growth hormone has been administered to animals in an attempt to evaluate its effect on normal and abnormal growth. Neoplasms of organs other than the pituitary gland occurred much more frequently in rats injected with growth hormone than in the controls.^{6,7,8} In hypophysectomized rats injected with growth hormone, there was an almost complete absence of neoplasms. This is in contrast to the occurrence of many different neoplasms in the intact rat which were similarly treated. It would appear that the presence of the pituitary gland and hence its secretions are necessary in the production of the neoplasms resulting from the administration of growth hormone. The long continued administration of growth hormone has been shown to produce morphologic alterations in the various component cells of the anterior pituitary. Hence,

large amounts of growth hormone and the altered physiology of the anterior pituitary are two important factors in the occurrence of neoplasms.¹⁰

Administration of growth hormone to humans with advanced breast cancer has demonstrated acceleration of the disease process. When administered to one patient following hypophysectomy an increased urinary calcium excretion occurred.^{11,12} The administration of growth hormone to two patients with advanced prostatic cancer resulted in an increased urinary calcium excretion, increased serum acid phosphatase and marked increase in pain.¹³

B. Postmenopausal women: The factors controlling the maintenance of tumor growth in the postmenopausal patient are not as clearly defined. It appears that the stroma about the tumor is important in the rate of tumor growth and response of the tumor to hormone therapy.¹⁴ It has also been postulated that in the postmenopausal period the production of growth hormone by the pituitary gland is increased.

Hormonal Therapy of Breast Cancer

There is indisputable evidence that either the administration or deprivation of steroid hormones profoundly alters advanced carcinoma of the breast. Their use as therapeutic agents is limited to those cases in which other accepted measures have failed or are not applicable because of the extent of the spread of the tumor. More recently it has been demonstrated that hormonal therapy may be employed in certain inoperable cancers of the breast and thus make them amenable to surgical removal.¹⁵ The modes of action of alterations of the hormonal status are subtle as indicated by the considerable variability in the responses of apparently identical lesions among comparable patients to a single form of therapy. Of further importance is the fact that in different individuals several hormonal agents are capable of producing essentially similar effects, though not to the same degree, on the various manifestations of breast cancer. Obser-

vations suggest that the metabolic pathways and capacities of the hormones at any given time may be governed by the current physiologic status of the patient. It is generally agreed that the relatively slower growing tumors respond best to hormonal alteration therapy. Cases of primary carcinoma of histologically high malignancy are evidently poor candidates for hormone therapy. Excellent regressions, however, have been obtained in several of the most malignant recurrent tumors, indicating that other factors played an important role in the therapeutic response.¹⁴ An attempt is made here to set forth the known methods of hormonal therapy of advanced breast cancer. By familiarity with these methods the rationale for total hypophysectomy in breast cancer can be more clearly understood. Again, the separation of the patient into two groups, premenopausal and postmenopausal, is made.

A. Premenopausal state:

1. Castration: The demonstration that estrogens are necessary for the maintenance of the growth rate of breast cancer provides a physiologic basis for treatment. Castration has become an accepted addendum to the treatment of cancer of the breast in advanced stages in the permenopausal woman. Most reports indicate that approximately 30% of patients obtain palliative benefit from castration although some workers claim improvement in as many as 56% of cases. There is general agreement that prophylactic castration does not increase the curability rate of those patients in whom radical mastectomy is performed for a cancer apparently confined solely to the breast or regional lymph nodes. It would appear that therapeutic castration should be reserved as another weapon to be employed at the time when metastases appear. Either surgical oophorectomy or radiation of the ovaries has been employed as the method of castration. Oophorectomy is preferable if a rapid clinical effect is desirable because of severe symptoms due to the metastatic disease. Improvement following castration will usually occur

within two months. Once improvement occurs, no additional hormonal therapy need be employed. In those patients showing no change after 3 to 6 months, further therapy to be considered would be the same as employed in postmenopausal type patients.

2. Androgens: The administration of adequate amounts of androgenic hormone to the premenopausal women leads to effects similar to those seen after castration. Testosterone propionate, 300 mg. weekly in 3 divided doses, is the most commonly employed preparation. It appears to be most efficacious in patients with osseous metastases. Soft tissue lesions may undergo regression though the incidence of regression is less than that noted in patients with only osseous lesions. The mean survival of patients responding to testosterone propionate is twice that of patients not responding to such treatment.¹⁶ Androgenic hormones have been employed in conjunction with ovarian radiation to hasten suppression of ovarian function in patients too ill for surgical oophorectomy. Androgenic hormones are not as effective as surgical or radiation castration in the same age group.

3. Bilateral total adrenalectomy: Bilateral adrenalectomy will induce significant objective remissions in patients with advanced breast cancer,^{1,17} but it appears that less than 40% of women with breast cancer will respond favorably to adrenalectomy. There is a close correlation between the response to castration and the subsequent response to adrenalectomy. The data further indicates that failure to respond to castration means there will be failure to respond to adrenalectomy.¹ The practice of combined bilateral oophorectomy and bilateral adrenalectomy should be condemned. To date there is no evidence that improvement so attained is any more than would be expected with castration alone. It would appear more appropriate that total adrenalectomy be reserved for those patients who previously have demonstrated a regressive response following castration.

4. Cortisone: Massive doses of cortisone administered orally have been employed in advanced breast cancer in an attempt to suppress the pituitary gland and produce secondary atrophy of the adrenal cortex. Objective regressions similar to those noted with other forms of hormone therapy have been observed. To date it would appear that cortisone in doses of 300 mg. a day should be employed in patients previously castrated, but uncontrolled and who are poor operative risks for bilateral adrenalectomy or hypophysectomy, or who refuse these radical surgical procedures. Maintenance of control of tumor growth and an unusual sense of well being has continued up to one year in such patients. In others, cortisone has been of excellent palliative value because of the euphoric effect and the reduction of inflammatory processes. Doses of 50 to 100 mg. a day have not been completely evaluated, but should be in view of the fact that the adrenalectomized or hypophysectomized patient receives supportive therapy in this amount. Some subjective improvements in such patients could be the result of the steroid supplementary therapy.

5. Estrogenic hormones: Estrogenic therapy in women castrated premenopausally several years earlier may produce regressions of breast cancer similar to that seen in older women who have had a spontaneous menopause. Furthermore, in young women who had no response to castration, improvement may occur when estrogenic therapy is employed. However, the degree of this response is usually less marked than with other forms of therapy. Regression of breast cancer has occurred in premenopausal women in the presence of active ovarian function when 1000 mg. of stilbesterol was administered daily.^{2,15} These findings suggest that inhibition of pituitary growth hormone or gonadotropic factors play a role in breast cancer.

6. Pituitary suppression: Attempts to produce pituitary suppression by radiation of the pituitary

gland have been attempted. The administration of as much as 10,000 r tissue dose to the pituitary gland in women with metastatic breast cancer resulted in no clinical or laboratory evidence of hypopituitary function, nor was the growth of the neoplasm effected.¹⁸

B. Postmenopausal patients:

1. Estrogens: Estrogenic hormones (stilbesterol 15 mg. daily) are indicated primarily for advanced breast cancer in postmenopausal women regardless of the chronological age of the individual. The best results, however, are generally attained in elderly women. In postmenopausal women, estrogens are significantly superior to androgens in their objective favorable effect on the soft tissue manifestations of breast cancer and essentially equal in osseous metastases.

2. Androgens: Androgens yield a high incidence of symptomatic relief with a considerably disproportionate and relative low remission rate of the physical characteristics of the cancer. The increased urinary excretion of estrogens during the administration of androgenic hormones may explain the favorable effects occasionally noted in soft tissue breast lesions in the postmenopausal woman.

3. Cortisone: Adrenal steroid hormone therapy has been employed in the postmenopausal woman largely as a palliative measure to improve the appetite and attain an increased feeling of well being. There appears to be little objective regression of the tumors during administration of this compound.

4. Bilateral adrenalectomy and hypophysectomy have not been carried out in a large number of postmenopausal women. The operative risk would appear to be too great in this age for the limited improvement to be gained.

The Rationale of Surgical Hypophysectomy

It would appear that the pituitary gland is a source of hormonal factors involved in the acceleration or maintenance of tumor growth in breast cancer. It has been demonstrated that growth hormone has a direct effect on promoting

the tumor growth. ACTH stimulates the adrenal glands to produce hormonal compounds stimulating to tumor growth, and the pituitary gland may contain other factors as yet unknown which in themselves maintain tumor growth. It has been postulated that the ameliorative effects of the administration of sex hormones in patients with advanced cancer of the breast may be due to the fact that in massive doses these hormones depress pituitary function and produce a "chemical hypophysectomy."¹⁹ To substantiate this the incidence of peripheral malignancy in Simmond's disease has been recorded.²⁰ Cancer of the breast or ovary have not been observed in association with Simmond's disease while cancer of the cervix, thyroid, and other organs has been noted. This is a further basis for the possible advantage of surgical total hypophysectomy as a therapeutic measure for advanced cancer of the breast.

In a woman with metastatic breast cancer previously castrated, total hypophysectomy would appear to be preferable over bilateral adrenalectomy. Hypophysectomy would attain the same end result as adrenalectomy in addition to removal of such factors as growth hormone; total hypophysectomy would appear to be more easily tolerated with less postoperative discomfort than bilateral adrenalectomy; total hypophysectomy would produce secondary atrophy of accessory adrenal glands which may not be removed in the adrenalectomy procedure. Accessory adrenocortical nodules have been described since 1740. Since then, portions of the adrenocortical tissue have been related to the liver, pancreas, mesentery, and genital tract. 32% of 100 consecutive autopsies revealed accessory adrenal tissue. One-half of the patients had both adrenal medulla and cortical tissue, the remaining half had cortical tissue only.²¹

Some physicians might question whether the results to be attained justify the radical procedure of hypophysectomy. It is the opinion of this investigator that the procedure will contribute to our information regarding the mechanisms of growth of breast cancer and

TABLE I. Surgical Hypophysectomy (literature)

Case #	Investigator	Disease	Year of Operation	Duration of Life Post-operative	Result
1	Lisser (23,24)	Cushing's	1933	6.5 years	Temporary regression 1 year
2	Elden (25,26,27,28)	Epilepsy	1935	6. years	0
3	Chabanier (29)	Diabetes Mellitus	1934	0.5 year	Died of Tbc., less insulin
4-5	Luft, Olivecrona (30,31)	Cushing's	1951	0,2,3 days	0
6	"	"	"	Alive 2 years	Improved, pregnant
7	"	Diabetes Mellitus	"	Alive 2 years	Improved, less insulin
8-10	"	"	"	0,2,30 days	0
11-12	"	Malignant Hypertension	1952	2,5 months	Slight improvement
13-17	"	"	"	0	Died of acute cerebral edema
18	"	Cancer Prostate	"	4 months	Improved
19	"	Hypernephroma	"	3 months	0
20	"	Chorionepithelioma	"	5 months	Improved! Died of aneurysm.
21-23	"	Cancer Breast	"	3,5,8 months	0
24-28	"	"	"	-	(Recent operations)
29	"	"	"	Alive 8 months	Improved
30	Perrault (32,33,34)	"	1952		Improved

31	- - - - (35)	Malignant Hypertension	1952	0	0
32	Schutte (36)	Cancer Breast	1952	Alive 13 months	Improved
33	Knowlton (37)	Adrenal Carcinoma	1951	7 weeks	0
34	Shimkin (38)	Malignant Melanoma	1951	9 weeks	0
35-36	Scott (39)	Cancer Prostate	1951	1,9 months	0
37-38	"	Cancer Prostate	1951-2	5,12 months	Improved, Died CVA; p. infarct
39-46	Kennedy (13)	Cancer Breast	1952-3		(present report)
47-49	Pearson (11,40)	Cancer Breast		Alive	Improved
50-57	"	"		-	0
58-65	"	"		Alive	(Recent operations)
66-67	Kinsell (41)	Diabetes Mellitus	1953-4	3,4 months	0
68-69	"	"	"	Alive 3,5 months	Improved
70-73	Kennedy, et al.	Cancer of Breast	1954-5	Alive 4,8,14 months	Improved
				12 months	Improved
				2,4,22,25,41 days, 4,9 months	0
				Alive 2 months	(Recent operation)

concomitantly contribute to the investigation of the metabolic aspects of the pituitary gland. Furthermore, it is possible that in the future linear acceleration radiation units might be sufficiently developed for human use to offer a possible means for eradication of the pituitary gland by radiation therapy. Familiarity with the secondary changes of pituitary removal can be attained in the meantime by surgical methods. Research on human beings, of course, involves unique hazards and responsibilities. For those interested in the problem of human research, I would recommend an excellent discussion of the problem by Shimkin, et al.²²

Total Hypophysectomy

(Review of the Literature)

Total hypophysectomy has long been considered in the treatment of various diseases. To date, there are 69 case reports available in the literature which have been summarized (Table I). Many others have been performed, but as yet are unreported. The procedure has been carried out for Cushing's disease,^{23,24,30,31} epilepsy^{25,26,27,28}, diabetes mellitus^{29,30,31,41}, malignant hypertension,^{30,31,35} adrenal carcinoma³⁷, prostatic carcinoma^{13,30,31,39}, hypernephroma^{30,31}, chorionepithelioma^{30,31}, and malignant melanoma³⁸. Improvements have been noted in Cushing's disease, diabetes mellitus, malignant hypertension, prostatic carcinoma, chorionepithelioma, and carcinoma of the breast. Lisser, Elden, and Chabanier reported hypophysectomies in 1933 to 1935. It was not until the availability of ACTH or cortisone therapy that more numerous reports occur beginning in 1951.

38 cases of advanced carcinoma of the breast with surgical hypophysectomy have been reported in the literature. An additional 21 have been carried out by one investigator⁴², but are as yet not reported. All investigators have demonstrated regressive alterations in the tumor. Luft and Olivecrona^{30,31} reported 9 cases. Three died without improvement at 3, 5 and 8 months postoperatively, 5 patients were too recently

operated on to evaluate, and 1 patient 49 years old was alive 8 months post-operatively and demonstrated striking regression of skin metastases on the anterior chest wall. Perrault^{32,33,34} reported 1 case in which pulmonary metastases regressed. Schutte³⁶ reported a 52 year old woman who was alive 13 months after hypophysectomy with marked relief of pain, and rehabilitation. Pearson and West^{11,40} reported that 11 of 19 patients had lived sufficiently long following the hypophysectomy for evaluation. Three of these 11 patients demonstrated objective regressions in the tumor. Kennedy¹³ reported 8 patients with carcinoma of the breast. These are discussed in the present report.

Selection of Patients with Advanced Breast Cancer for Total Surgical Hypophysectomy

Earlier observations on the response of advanced breast cancer to hormonal alterations have provided a physiologic basis for selection of patients for hypophysectomy. At present it would appear unjustified to carry out hypophysectomies in premenopausal women with active ovarian function, since the regression rate would appear to be no greater than with castration alone. The patients selected for hypophysectomy have been those previously castrated. The castration in some instances was done before the onset of known metastases and in others was carried out for treatment of metastatic lesions. In both instances one would expect to have an increased pituitary function. Postmenopausal women under the age of 60 who do not have evidence of active ovarian function by vaginal smear (cornification of the mucosa representing estrogenic effect) also would appear to be suitable candidates for this procedure.

As yet there is no evidence that the pathologic type of the tumor is directly correlated with tumor response. Since regressions under other forms of hormone therapy have occurred in the most malignant appearing lesions it is apparent that this criteria alone is not satisfactory. A similar experience has been recorded in patients undergoing

adrenalectomy in that there is no better than a 75% correlation. Even more significant was the lack of correlation, in that well differentiated tumors failed to respond to adrenalectomy and some anaplastic tumors did respond.¹ Clinically, however, the inflammatory type tumor or the tumor with rapid progression does not respond well to most forms of hormone therapy and would not be expected to respond to hypophysectomy. Our experience supports this supposition.

Contraindications to hypophysectomy can be stated, based upon our present experience. Obviously, patients who are poor operative risks cannot be done. Patients with massive pleural effusion or extensive pulmonary metastases and patients with unexplained tachycardia (frequently due to extensive disease) are regarded as poor operative risks. When the liver is involved with massive metastases, it would appear that careful consideration should be made before subjecting these patients to surgery. The tolerance of anesthesia is poor and from previous experience with hormone therapy the patient must have a minimum life expectancy of 2 months to allow objective improvement to occur. In view of the more slow regression rate following hypophysectomy, patients with extensive liver metastases should not have the procedure. From a technical point patients with extensive skull metastases or meningeal metastases are poor candidates because of bleeding from the vascular tumor. Patients with massive tumor involvement of the bone marrow frequently have thrombocytopenia. In this instance the procedure should not be carried out because of possible intracranial bleeding.

The potentialities of therapy of breast cancer by hormonal alteration are becoming increasingly obvious and better defined. Still, one must reiterate that surgery and irradiation remain the optimum methods available for more permanent control of localized and accessible manifestations of breast cancer.

Procedures for Evaluation of Tumor Response and Degree of Completeness of the Hypophysectomy

The criteria for evaluating tumor response are those established by the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association. Though relief from pain and increased well being are important, only objective responses are regarded as a result of the hypophysectomy procedure.

Metabolic observations in the Metabolic Research Unit have been carried out in 7 of the 12 patients operated upon. The measurement of calcium and phosphorus excretion, and serum calcium, phosphorus and alkaline phosphatase have been employed as a means of measuring the rate of tumor growth or tumor regression.

Removal of the pituitary also affords a valuable source of information regarding the metabolic and endocrine changes occurring secondary to removal of the gland. There is no established test which records the complete removal of the pituitary gland. Hence a measure of the function of the end organs has been made to evaluate the degree of decreased control by the pituitary.

1. Thyroid: The basal metabolism rate and radioactive iodine tracer study have been employed to evaluate thyroid function.

2. Adrenal: The ACTH eosinophil test, urinary 17 ketosteroids, glucose tolerance test, blood pressure, and serum electrolytes have been employed as measures of adrenal functions.

3. Ovaries: Since most of these patients have no ovaries, no test for ovarian function was carried out.

4. Pituitary: Assay of follicle stimulating hormone and the glucose tolerance test have been employed as a measure of the function of the pituitary gland. A recording of the water balance (posterior pituitary factor) has been frequently employed as a measure of total pituitary removal. However, the lack of sufficient investigations in humans totally hypophysectomized prevents definite conclusions from being drawn regarding the degree of completeness of

removal of the pituitary gland.

Preoperative Management

1. Preliminary tests: In addition to the usual preoperative evaluations of a patient undergoing surgery, specific factors are necessary. A recording of the status of the eyes and visual fields is carried out. An x-ray of the skull is obtained to establish the position of the pituitary fossa and the presence of skull metastases. Multiple blood pressure recordings are made several days preoperatively to obtain a base line of the patient's normal blood pressure. Bleeding and clotting time and platelet count must be normal. Serum electrolytes and BUN are obtained prior to the administration of any steroid therapy and on the morning of the operation.

2. Anesthesia: Intratracheal anesthesia employing pentothal, curare and nitrous oxide has been employed routinely. No anesthetic complications have arisen. It would appear that adequate management of hormonal factors is sufficient to allow ease of anesthesia in this procedure.

3. Hormone therapy: The present method of preparation of the patient for surgery is described. Cortisone is begun 2 days preoperatively in a dose of 100 mg. every 12 hours intramuscularly. Cortisone has been used entirely; not ACTH. The latter is dependent upon the presence of a normal adrenal function which may not be present because of metastases in the adrenal glands. Desoxycorticosterone acetate, 5 mg. intramuscularly, is begun 1 day prior to the operation. The morning of surgery the patient receives 100 mg. of cortisone intramuscularly as previously scheduled, 5 mg. of DOCA intramuscularly and 100 mg. of cortisone orally.

Hypophysectomy Operative Technique

The incision is the usual incision made for transfrontal craniotomy: the so called concealed incision above the hair-line with the scalp flap turned forward and lateral. A bone flap is then reflected laterally, pedicled on the temporal muscle. This bone flap extends to

the midline and forward to just above the frontal sinus. In all cases the operation has been done on the right side.

The exposed dura is opened by reflecting a flap medially. This dural flap is 3 1/2 to 4 centimeters wide and extends from the anterior edge of the bone flap back almost to the coronal suture. A block of the anterior medial portion of the frontal lobe is then removed extending directly down through the lobe from the edges of the sectioned dura and extending forward to the frontal pole. The posterior edge of this excision comes directly down on the optic chiasm with the anterior communicating arteries overlying it. Thus, wide exposure of the pituitary fossa is attained without any retraction of the remaining portion of the frontal lobe. Other investigators have employed a procedure retracting the intact frontal lobe which results in trauma of the lobe and may produce post-operative brain edema. This complication has necessitated decompression procedures. Resection of the frontal lobe eliminates the complication of edema and increased cranial pressure.

To obtain better exposure of the anterior part of the sella turcica, the tuberculum sellae and medial part of the medial clinoid processes are removed. This is accomplished by perforating the tuberculum sellae with a small chisel and then rongeur away the bone.

With a root retractor the optic chiasm is gently elevated to expose the pituitary stalk passing backwards and upwards behind the chiasm. The stalk is picked up with a hook and held forward while a silver clip is put on it above the hook and then the stalk is cut.

The diaphragma sellae has an opening of variable size through which the stalk passes. This opening is enlarged by making with a knife two or more radial cuts in the diaphragm from the opening for the stalk toward the periphery of the sella. The upper surface of the pituitary is thus widely exposed, and an attempt is then made to separate it

around its periphery and shell it out of the fossa. Sometimes it is possible to shell out most of the pituitary in one smooth walled piece, but invariably some fragments remain attached to the walls, especially in the anterior part of the fossa. These are then curetted out. Most of the wall is then easily inspected and seen to be free of gross remnants of pituitary. The undersurface of the margins of the diaphragma sella cannot be seen, and one must depend upon the curette to get all fragments from this site. In some of the patients the empty fossa was swabbed with a cotton pledget soaked with Zenker's solution.

There has been no difficulty with hemorrhage in any case of hypophysectomy for breast carcinoma. Hemorrhage has been so moderate that good visualization has been possible throughout the procedure of the removal of the gland and a dry cavity could be well inspected after removal of the pituitary. Estimated blood loss as a rule has not exceeded 500 cc.

Of particular importance in the surgical technique is the relationship of the optic chiasm and the pituitary body. Four arrangements have been described:⁴³

A. Chiasm in the optic groove of the sphenoid with the hypophysis and infundibulum posterior to the chiasm. 5%

B. Pituitary underlying the chiasm both anteriorly and posteriorly, the chiasm being markedly posterior to the optic groove. 12%

C. Pituitary completely anterior and inferior to the chiasm and protruding laterally beyond the chiasm. 79%

D. The entire mass of the pituitary anterior to the chiasm with no lateral protusion. 4%

Of the patients undergoing hypophysectomy in this series, special note was made of the position of the optic chiasm and pituitary body. In 4, the position of the optic chiasm was that most commonly noted: in 3 the optic chiasm was

far posterior to the pituitary body and the optic nerves were unusually long; in 2 the optic chiasm was anterior with only a few millimeters between the anterior border of the chiasm and the tuberculum sellae.

The position of the optic chiasm far anterior in the optic groove makes it necessary to consider resection of one optic nerve in order to retract the chiasm and gain access to the pituitary fossa. In one patient with carcinoma of the prostate not reported in this series, the chiasm was so far prefixed as to necessitate section of the right optic nerve.

Postoperative Management

A. Immediate: Cortisone, 200 mg. every day intramuscularly, is administered until the patient can take oral cortisone. The dose is gradually reduced to a daily maintenance level of 50 to 75 mg. DOCA, 2 mg. intramuscularly, is given daily until the patient is able to take oral linguets. Parenteral fluid administration is limited to no more than 2500 cc. daily in an attempt to avoid overloading with water and possibly contributing to cerebral edema. If a decrease in blood pressure is encountered, intravenous hydrocortisone has been employed. However, in most instances the hypotension is on a cardiovascular basis; levophed has been employed in these instances. Most patients have a postoperative fever for 2 or 3 days. Prophylactic antibiotic therapy has consisted of streptomycin and penicillin in all instances.

B. Late: Most patients are able to take fluid the first postoperative day and begin eating the second or third day. Every effort should be made to place medication on an oral basis. Within one week postoperatively thyroid extract, 60 mg. daily, is begun and later increased to 120 mg. daily. No pitressin is administered until the end of at least the second week. Though the patients have an immediate polyuria and polydipsia it would appear preferable to await the permanent establishment of polyuria

before instituting pitressin therapy. Supplementary NaCl is necessary in some cases.

Complications of Surgery

It is to be expected that with major surgery of this sort certain complications arise. Excluding those factors that occur in any patient who is a poor operative risk, some factors are pertinent to this procedure.

1. Eye: In 2 patients gross visual disturbance has occurred. In one this was immediate postoperatively and consisted of a permanent loss of peripheral vision of the right eye and pain in the orbit. A second patient who developed meningitis 6 days postoperatively concomitantly had loss of vision in the right eye. This persisted for 2 months, at the end of which time some light perception has appeared.

2. Headache: Headache occurs postoperatively in almost all patients but the intensity varies considerably. The aching persists for a few days.

3. Rhinorrhea: Two patients have developed postoperative drainage of spinal fluid from the nose; the result of perforation of the sphenoid sinus mucous membrane when the bone of the tuberculum sellae was removed. One of these patients later developed meningitis. The rhinorrhea disappeared following recovery of the meningitis. A second patient had rhinorrhea for approximately one week which subsided spontaneously without complication. There has been no persistent rhinorrhea in any patient.

4. Infection: Three patients have developed postoperative meningitis. The first patient had uremia and confusion; meningitis was not recognized. On autopsy examination there was an E. coli meningitis with localized abscess at the base of the brain. A proteus species meningitis developed in a patient with rhinorrhea. Fortunately this was sensitive to chloromycetin. An initial course of therapy was carried out but a relapse occurred and a second course of

antibiotic therapy resulted in cure of the meningitis. The third patient developed a paracolon meningitis 6 days postoperatively but recovered following chloromycetin, achromycin and sulfadiazine therapy.

5. Personality changes: In the week following hypophysectomy seven patients demonstrated a definite euphoria. This may be secondary to the large dose of cortisone administered or due directly to the operative procedures. In all cases it was temporary. In 3 of these patients a temporary personality change occurred resembling that of patients having had lobotomy procedures. They were belligerent, confused and euphoric. In no patient has there been a permanent personality alteration.

6. Polyuria and polydypsia: Temporary polyuria and polydypsia has occurred in 8 of 12 patients in the immediate postoperative period. In 5 patients who survived more than a period of 1 month a permanent polyuria and polydypsia has occurred. This occurred in spite of the fact that in 2 of these patients no pituitary cells were present in the pituitary fossa on autopsy examination. Interpretation of the water balance will be made later.

Tumor Response

Evaluation of the tumor response is divided into two factors - subjective response and objective response (Table II). No evaluation of the tumor response is made in 2 patients who died less than 4 days postoperatively. In one patient there were no initial complaints and hence subjectively she had no improvement. One patient on massive cortisone therapy had marked feeling of well being before as well as after surgery. A mild subjective response was noted in 2 patients, moderate response in 2 patients and a marked subjective response in 3 patients. In the latter this consisted of pain relief, increased feeling of well being, increased appetite, weight gain and rehabilitation.

Objective response can be evaluated

TABLE II -- Surgical Hypophysectomy in Breast Cancer

Case #	Age	Duration P. O. *dead	Response	
			Subjective	Objective
1	50	22 d. *	+	0
2	56	4 d. *		
3	43	9 MO.*	++	0
4	49	41 d. *	+	0
5	45	12 MO.*	++++	++++ bone, lung skin, liver
6	43	25 d. *	++	(+) ulcer
7	49	<u>14 MO.</u>	++++	++++ bone
8	52	<u>8 MO.</u>	++++	++++ bone, lung skin, liver
9	55	4 MO.*	0	0
10	46	<u>4 MO.</u>	-	+++ skin
11	44	<u>2 MO.</u>	-	?
12	57	2 d. *		

in 9 patients. One patient was only recently operated on. In 4 patients living 22 days, 41 days, 4 months and 9 months no objective response occurred. One patient demonstrated epithelization of an ulcer of the anterior chest wall but died on the 25th day. Four patients demonstrated striking regressions in the disease process.

These regressions have consisted of recalcification of osteolytic metastases, decrease in size of pulmonary lesions, disappearance of skin lesions and decrease in size of the liver and reduction of an elevated alkaline phosphatase due to liver disease.

Duration of Response

The duration of response cannot be fully evaluated at the present time. In 2 patients, however, marked improve-

ment was maintained for 6 and 7 months before evidence of reactivation of the disease process occurred. One patient, 14 months postoperative, still maintains all evidence of improvement. The 4th patient 4 months postoperative has retained the improved state. The patients alive at present have survived 2, 4, 8 and 14 months since the operation.

Metabolic Investigations

Metabolic investigations were carried out in 7 patients undergoing hypophysectomy. In 4 of these sufficient studies were obtained to demonstrate the physiological alterations that occur postoperatively in evaluating the response of the tumor and changes in the endocrine glands.

1. Tumor response: It would appear that the serum calcium, phosphorus and

alkaline phosphatase and the urinary calcium and phosphorus excretion are reliable indices of the measure of tumor response following hypophysectomy, similar to that accompanying other forms of hormone therapy in breast cancer. Patients who improved demonstrated a decrease in the initially elevated serum calcium and a decrease in urinary calcium excretion. Concomitantly there was an elevation of serum alkaline phosphatase during the period of osseous repair. Later studies revealed that reactivation of the disease process was associated with an increased urinary calcium excretion and an increase in the serum calcium and phosphorus.

2. Thyroid: In 2 patients (cases 3 and 5) the status of the thyroid was followed postoperatively before the administration of thyroid hormone (Table III and IV). Both patients demonstrated a striking decrease in the basal metabolism rate to values of -40 and -55.

The radioactive iodine tracer test decreased to hypothyroid levels. In Case 3, on instituting thyroid therapy after 121 days, the BMR returned to a normal value. It is apparent that the thyroid function in both these patients decreased from normal to an athyroid state due to the removal of thyroid stimulating hormones. In the remaining patients thyroid therapy was begun immediately postoperatively in order to avoid the clinical symptoms of hypothyroidism.

3. Pituitary: There is no direct assay of pituitary function which is sensitive enough to demonstrate total pituitary removal. Follicle stimulating hormone assays were carried out as a crude measure of pituitary function. It would be expected that most of these patients who were recently postmenopausal or castrated, the level of follicle stimulating hormone would be increased. However, the administration of androgenic hormones prior to hypophysectomy inhibited

TABLE III -- Case 3. Z. S. Age 43 Breast Cancer

Thyroid Status + Hypophysectomy

Days	BMR	I ¹³¹ Uptake
Pre operation	-9%	35%
21	-35	21
42	-19	
77	-25	11
117	-40	8
121	Thyroid therapy begun	
131	-20	
142	-20	
159	-3	

TABLE IV -- Case 5. L. K. Age 45 Breast Cancer

Thyroid Status + Hypophysectomy

Days	BMR	I ¹³¹ Uptake
-9	-9	59%
-2		62%
Operation - - - - -		
29	-32	16%
47	-55	19%
69	-32	

the production of follicle stimulating hormone and such patients demonstrated no assayable FSH in the urine (Table V). In those patients with normal or elevated FSH assays prior to hypophysectomy there was a disappearance of assayable FSH in

the urine postoperatively (Table VI). This disappearance presumably is due to the removal of the pituitary gland but the administration of supplementary cortisone therapy might in itself have some inhibiting effect.

TABLE V -- Case 6. B. S. Age 43 Breast Cancer

Period (3 day)	Cortisone (mg/day)	17 - KS (mg/d.)	FSH. (m.u.)
3		5.1	< 6
4	100 i.m.	7.0	< 8
5 - - - - -	250 i.m.	- - - - -	Hypophysectomy - - - - -
6	130 i.m.	8.9	
7	100 i.m.	11.7	< 8
8	80 oral	13.4	
9	50 oral	6.2	
10	"	5.9	
11	"	6.7	
12	"	6.2	< 8
13	Died	"	

TABLE VI -- Case 4 G. M. Age 49 Breast Cancer

Period (3 day)	Cortisone (mg./day)	17 - KS (mg./day)	FSH. (m.u.)
4		2.9	64
5	100 i.m.		
6	125 i.m.	0.7	24
7 - - - - -	200 i.m.	- - - - -	Hypophysectomy - - - - -
8	50 i.m.		
9	50 oral	6.2	< 8
10	"	4.7	
11	"	3.7	
12	"		
13	"	5.0	
14	"	2.5	
15	"	1.2	< 8
16	"	1.2	< 8

4. Adrenals: The status of the adrenal gland in patients with advanced breast cancer might be expected to be in a hypofunctioning state because of the debilitated condition of the patient. It has been demonstrated that the ACTH eosinophil test is not a reliable index of adrenal function. The failure of this test was demonstrated in an unfortunate manner in the first total hypophysectomy we performed which was done in a patient with cancer of the prostate. This patient demonstrated a decrease of 50% of the eosinophils following intravenous ACTH, but at autopsy the adrenal glands were totally replaced by tumor tissue.

The urinary 17-ketosteroid assay was employed as a measure of adrenal function. Preoperatively all the patients showed low normal or low values. Immediately following the operation there

usually was a slight increase in 17-ketosteroids because of the large dose of administered cortisone. Subsequently the 17-KS decreased to normal or low values, dependent in part upon the dose of cortisone employed as maintenance therapy (Tables V and VI). In one patient with a total bilateral adrenalectomy the preoperative 17-KS was 4.5 mg. per 24 hours while receiving 50 mg. of cortisone. Postoperatively on maintenance therapy of 37 1/2 mg. per day of cortisone, the 17-KS ranged from 2.5 to 5.5 mg. per day. The 17-ketosteroids present would appear to be largely due to the cortisone administered. Since these patients are maintained on supplementary cortisone therapy, evaluation of the postoperative adrenal state has been difficult. It is obvious that by omitting cortisone the blood pressure falls. The serum electrolytes are not significant, because a disturbance might reflect

changes in water balance due to diabetes insipidus.

5. Polyuria: The absence of the posterior pituitary hormone, pitressin, results in polyuria and secondary polydypsia. It has frequently been stated that the presence of anterior pituitary lobe cells are necessary for this phenomena. All patients but one surviving one month have demonstrated permanent polyuria and polydypsia of varying intensity. In view of the fact that in two such patients an autopsy revealed no detectable anterior pituitary cells, we questioned the accuracy of the assumption that anterior pituitary cells are necessary for the presence of polyuria. It would appear that the picture of diabetes insipidus cannot be used as a criteria for total hypophysectomy. Considerable alterations of interest have occurred in our patients with polyuria. Intensive investigations are being carried out at the present time to further evaluate the problem of electrolyte and water balance in the hypophysectomized human.

Pathological Data

Microscopic examination of the pituitary glands will be studied later through the cooperation of the Department of Anatomy. Two features of interest in specimens removed at the time of the operation were noted. In one, section of the frontal lobe revealed tumor metastases in the brain tissue. The pituitary of a second patient revealed the presence of cancer metastases within the pituitary tissue.

Autopsy examinations have been carried out in 4 of 8 patients who have died. The findings in 3 of these autopsies are of interest. Examination of the pituitary fossa revealed no pituitary cells in 2 patients and a rare anterior pituitary cell in one patient. The thyroid glands were small. The adrenal glands were absent in one patient (adrenalectomy), small in one patient and replaced by tumor in the third patient. All patients showed extensive metastatic disease.

Discussion

Alterations of the hormonal status of the individual may profoundly influence the course of advanced breast cancer. Such alterations probably occur spontaneously and may account for the wide variations in the course of untreated breast cancer. The modes of action of hormonal therapy are subtle. Even though the precise mechanisms cannot be defined, observations suggest that tumor metabolic pathways are governed by the current physiological status of the host. In advanced breast cancer it appears that the maintenance and growth of the cancer is dependent upon hormonal factors of the ovaries, adrenal glands and pituitary gland. No one of these factors alone is the major one. Yet the relative imbalance of the hormonal status attained by administration or deprivation of hormones may be truly as important as the total withdrawal or total administration of specific agents.

Total hypophysectomy has been attempted in advanced breast cancer because of the observations that estrogenic hormones androgenic hormones, and growth hormone are, under certain physiological conditions, a stimulus to the growth of breast cancer. The removal of the pituitary gland would thereby withdraw the stimulating factors and induce another hormonal imbalance. Twelve patients with advanced breast cancer have undergone total hypophysectomy. Four of these patients have demonstrated striking clinical regressions. One of these patients died one year after the hypophysectomy, 3 are alive and well 4, 8 and 14 months postoperatively.

One of the difficult problems encountered in the investigation of total hypophysectomy is the determination of the completeness of the surgical procedure. There is no sensitive test to measure the degree of success of hypophysectomy. However, in the patients investigated, hypofunction of the thyroid and adrenal glands have been demonstrated. Furthermore, disappearance of follicle stimulating hormone and the absence of

pituitary cells at autopsy in 2 of 3 examined patients suggests that the procedure employed in this investigation has been a total or at least near total hypophysectomy. Furthermore, to attain a desired tumor response it is quite possible that the presence of a few pituitary cells would have little or no importance; the relative decrease of pituitary function attaining the alteration in hormonal status necessary to produce the clinical regression.

Spontaneous remissions of breast cancer have frequently been referred to, but little investigation of such patients has even been reported. It would appear that the presence of metastatic tumor in the ovaries, adrenal glands and pituitary make possible the autogenous destruction of these glands. The relative decrease in function as a result of invading tumor might well explain the occasionally reported spontaneous remission.

Invariably, breast cancers showing profound regression undergo reactivation and at times appear to grow more rapidly than initially. There possibly occurs an adaptation of the more resistant tumor cells in a milieu initially rendered unfavorable to the growth of the tumor. A second favorable reaction may occur when the initial therapy is abandoned or when other hormonal therapy is instituted. The lesions thereby continue to be vulnerable by again shifting the physiologic or metabolic status of the host. Hypophysectomy is another means of altering the metabolic status of a patient with the chronic disease of breast cancer. Absence of response as in the case of initially unresponsive tumors might imply development of complete autonomy of the remaining cells. Reactivation of tumors initially responding to hypophysectomy might further be explained by the hypothesis that accessory pituitary tissue is functioning. Accessory anterior lobe tissue has been described in the pharyngeal mucosa, sphenoid bone, and within the sella turcica.^{44,45} A pharyngeal pituitary gland has been described in 51 of 54 autopsies.⁴⁶ In some cases of altered

structure or activity of the pituitary gland it cannot be denied that the pharyngeal pituitary gland may undergo structural alterations and serve as an endocrine organ.

Future potentialities of hypophysectomy will be important in investigations of cancer of the breast, prostatic cancer, chorionepithelioma, malignant hypertension and diabetes mellitus. It is quite possible that carcinomas of the ovary, thyroid and adrenal cortex might also be favorably effected by pituitary obliteration.

Conclusions

Clinical and metabolic observations provide a physiological concept for the medical treatment of advanced breast cancer in women. Hypophysectomy in selected patients offers another means of producing an alteration of hormonal balance with improvement in the disease.

Case Reports

Case 1. Age 50. A right radical mastectomy was done March, 1951. One year later osseous metastases appeared. The patient received x-ray castration, radiation therapy, an unsuccessful bilateral cervical cordotomy and testosterone therapy before admission to the University Hospitals in March, 1953. There was a right supraclavicular node, the liver was 4 fingers below the costal margin and extensive osteolytic metastases were present.

In an attempt to suppress pituitary function, stilbesterol 1000 mg. daily was administered for 48 days. There was an increased sense of well being and less pain. There was a decrease in serum phosphorus and an increase in serum calcium. The urinary calcium and phosphorus decreased slightly. The BUN increased and the serum alkaline phosphatase increased due to liver metastases. X-ray revealed a progression of the disease and the liver increased in size.

A total hypophysectomy was carried out May 18, 1953. Postoperatively there

was a decrease in pain and decrease in serum calcium and phosphorus and urinary calcium excretion. The patient died of a bacterial meningitis 22 days post-operatively.

Case 2. . Age 56. In 1948 a right radical mastectomy and postoperative radiation therapy were carried out. Four years later recurrence of the disease in the skin and sternum occurred. X-ray therapy was administered; later estrogenic hormone therapy was not successful and further radiation therapy was continued. In May 1953, the patient was admitted to the University Hospitals because of increasing dyspnea, bilateral pleural effusion, and numerous skin nodules on the anterior chest wall.

A total hypophysectomy was performed May 20, 1953. The patient died suddenly on the 4th postoperative day in a manner suggesting a pulmonary embolism or massive atelectasis of the lung. No autopsy was obtained.

Case 3. . Age 43. At age 41 a right radical mastectomy and bilateral oophorectomy were done for an ulcerative carcinoma of the breast present 2 years. One year later pulmonary metastases and osteolytic lesions in the pelvis were demonstrated. A bilateral adrenalectomy was performed December 29, 1952. The back pain disappeared, the patient gained weight, pulmonary lesions disappeared and osseous metastases recalcified. Metabolic data throughout the study period revealed further evidence of regression of the disease. Improvement was maintained for 9 months, at which time symptomatic and metabolic evidence demonstrated reactivation of the disease process.

A surgical hypophysectomy was carried out October 13, 1953, after a period of metabolic study. There was relief of pain and metabolic evidence of decreased rate of tumor growth. This consisted of a decrease in serum calcium, decrease in urinary calcium and an increase in the serum alkaline phosphatase. The im-

provement was maintained 2 months; the disease then progressed and the patient died 9 months after the total hypophysectomy.

Case 4. . Age 49. This woman underwent a spontaneous menopause at the age of 45. In June, 1952 a right radical mastectomy and postoperative radiation therapy were done. One year later the patient was admitted to the University Hospitals because of pain and massive skin recurrence over the anterior right chest wall. There were osteolytic and pulmonary metastases.

Total hypophysectomy was carried out December 5, 1953. The back pain decreased. The right arm became increasingly swollen and the skin disease of the chest progressed over the right shoulder. The patient was discharged from the hospital. At home the family decided that cortisone therapy was unnecessary and it was omitted. The patient died at home on the 41st postoperative day. Clinically, this patient had an erythematous type of carcinoma which would not ordinarily be expected to respond favorably to any form of hormone therapy.

Case 5. . Age 45. One and a half years before admission a right radical mastectomy and bilateral oophorectomy were performed. Sixteen months later, pain occurred in the left hip and the patient was admitted to the University Hospitals in November 1953. There were palpable nodules in the supraclavicular region, skin and scalp. X-rays revealed pulmonary nodules in the right lung and multiple osteolytic metastases.

A total hypophysectomy was carried out December 16, 1953. There was dramatic relief of pain. increased feeling of well being, increased appetite and increased strength. The skin nodules on the scalp decreased in size and other nodules disappeared. X-rays revealed a decrease in the size and number of pulmonary nodules and recalcification of osteolytic metastases. This regression

was maintained for 6 months.

Reactivation of the disease 6 months postoperatively was manifested by an increase in the size of skull metastases and weight loss. The patient was begun on testosterone propionate, 100 mg. 3 times weekly. There was rapid improvement following androgen therapy in that pain disappeared, there was an increased feeling of well being, increased weight, disappearance of cough and all remaining skin nodules disappeared. Improvement was maintained for 4 months at which time there was again reactivation of the disease with progression in the size of osseous metastases and increased pain. The patient died 12 months after hypophysectomy.

Comment: This patient demonstrated a definite response to hypophysectomy with relief of pain, increased well being, calcification of osteolytic lesions, almost total disappearance of skin lesions, and decrease in extent of pulmonary lesions. Progression of the disease occurred after 6 months. A second clinical remission was obtained by the administration of androgenic hormone therapy. It would appear this hormone mediated its effect directly on the tumor and not secondarily by pituitary suppression.

Case 6. Age 43. A left super-radical mastectomy was performed in May 1951 with postoperative x-ray therapy. A right radical mastectomy was carried out in April, 1952, and x-ray sterilization done. In January, 1953, metastases in the pelvic bone were noted. Stanolone therapy produced osseous recalcification. Nine months later there was reactivation of the disease with diffuse skin involvement of the anterior chest wall and pleural effusion. A second course of stanolone was unsuccessful.

A total hypophysectomy was carried out January 11, 1954. During the subsequent 3 weeks there was epithelization of the ulcer of the chest wall but the skin nodules did not decrease in size. The patient died suddenly 25 days fol-

lowing hypophysectomy with massive atelectasis of the left lung and left pleural effusion.

Case 7. Age 47. In April, 1951, a right radical mastectomy and postoperative therapy were done. In September, 1952, osseous metastases were first noted. The menstrual periods were regular. The patient was placed on a metabolic regime from March to July, 1953, and 1000 mg. of stilbesterol per day were administered orally. A decrease in urinary calcium excretion was demonstrated, but a steady progression of the disease occurred. X-ray castration was carried out in June, 1953, and testosterone propionate administered at the same time. There was marked decrease in pain, gain in weight and recalcification of the osteolytic lesions. Six months later there was a sudden exacerbation of the disease process with a rapid increase in the number of osteolytic lesions. Ribs were fractured or destroyed.

Total hypophysectomy was carried out February 1, 1954. Postoperatively the patient developed a proteus meningitis which responded successfully to chloromycetin. During the subsequent 14 months the patient has had an excellent clinical and objective improvement. There has been regeneration of destroyed ribs, calcification of osteolytic lesions, increased feeling of well being, and partial relief of pain. At present pain is limited to the low midback due to a fracture of a vertebral body. There is no evidence of active disease.

Case 8. Age 52. In February, 1951, a right radical mastectomy and postoperative x-ray therapy were done. In May, 1954, a left radical mastectomy and postoperative therapy were performed. During the course of postoperative therapy skin metastases were noted and the patient was admitted to the University Hospitals in August, 1954. There were extensive skin nodules over the arm, shoulder and thigh. The liver was palpable one finger breadth below the costal margin. X-rays revealed

pulmonary and osseous metastases. A spontaneous menopause began at age 47 and was completed by age 49.

A total hypophysectomy was done August 18, 1954. The patient demonstrated a remarkable total regression of all the skin metastases within 2 months. The large nodules disappeared and left a retracted area of skin. Pain was relieved, cough disappeared and the patient felt and looked very well. Seven months postoperatively there was evidence of some increase in size of osseous metastases and induration in the area of previous skin nodules. Though the patient still has no complaints and feels well, it is established that the disease has reactivated 7 months postoperatively.

Case 9. Age 55. A left radical mastectomy with postoperative radiation therapy were carried out in 1949. Concomitantly the ovaries were radiated. In February, 1951, a recurrent node was treated with radiation therapy. In October, 1952, the patient was treated with radioactive iodine for a classical thyrotoxicosis. In March, 1953, recurrent skin disease over the left chest wall appeared. Further radiation to the pelvis was administered to complete castration and the skin nodules of the anterior chest wall were radiated. These did not respond to castration or radiation and in January, 1954, stilbesterol therapy was begun and later changed to testosterone propionate. Despite hormone therapy the skin disease progressed in amount over the anterior chest.

A total hypophysectomy was done August 30, 1954. Postoperatively the tumor increased in size, ulcerated and progressed over the entire anterior chest. Four months postoperatively the patient was begun on testosterone propionate. The patient is presumed to be dead.

Case 10. Age 46. In June, 1951, a right radical mastectomy and postoperative x-ray therapy were carried out. One year later a prophylactic left mastectomy was done. In December, 1953,

cutaneous metastases first began. The patient was given x-ray castration and radiation of the skin nodules. During the subsequent 11 months improvement was maintained for the first 6 months.

Because of progression in the number of skin nodules and the presence of osseous metastases a surgical hypophysectomy was done December 6, 1954. Postoperatively the patient developed a paracolon meningitis which was successfully treated. Since discharge from the hospital the patient has gained weight and all skin nodules have disappeared. At the present time the patient is feeling well and the disease appears under control.

Case 11. Age 44. A right radical mastectomy and postoperative x-ray therapy were carried out in December, 1951. Two years later osseous metastases developed. In May, 1954, a bilateral oophorectomy was performed. Marked relief of pain and recalcification of osteolytic lesions occurred. This improvement was maintained for 4 months. There was sudden reactivation of the osseous disease with severe pain.

The patient was admitted to the University Hospitals on November 17, 1954. A complete metabolic study has been carried out since that date and is still in progress. The purpose of the study is to investigate the effect of cortisone alone, and subsequently hypophysectomy. With a dose of 50 mg. a day there was marked increase in urinary calcium excretion; with 300 mg. of cortisone there was a decreased excretion of urinary calcium but not to the normal range. It appeared that the disease could not be controlled with cortisone therapy and a total hypophysectomy was performed February 17, 1955. The patient tolerated the procedure unusually well. It is too early as yet to evaluate the response of this patient.

Case 12. Age 57. An extended left radical mastectomy was performed in March, 1954. One year later osseous

and liver metastases appeared. The last menstrual period was at age 54. The liver was enlarged 4 finger breadths below the costal margin.

A total hypophysectomy was carried out on February 28, 1955. The patient died the second postoperative day. It was apparent that this patient was a poor operative risk and the disease too extensive.

An additional patient was considered for hypophysectomy: M.V., age 56, had extensive osseous metastases. A craniotomy on April 14, 1954, revealed excessive bleeding because of scalp and meningeal metastases. The procedure of hypophysectomy was not attempted.

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II. MEDICAL SCHOOL NEWS

Coming Events

- April 18 - 20 Continuation Course in Allergy and Chest Diseases for General Physicians
- April 19 Clarence M. Jackson Lectureship; "A History of the Treatment of Bronchial Asthma;" Dr. Leslie N. Gay, Associate Professor of Medicine, Johns Hopkins University, Baltimore, Maryland; Mayo Memorial Auditorium; 8:00 p.m.
- April 20 Family Doctors' Day; Division of Neurosurgery; Hospital Dining Room; 12:15 p.m.
- April 27 Special Lecture; "Medical and Surgical Implications of Liver Regeneration;" Dr. L. Schalm, Director, Municipal Hospital, Arnhem, Holland; Todd Amphitheater, University Hospitals, 12:45 p.m.
- April 28 Phi Delta Epsilon Lectureship; "Newer Concepts in Psychosomatic Disease;" Dr. Adelaide M. Johnson, Professor of Psychiatry, Mayo Foundation, Rochester, Minnesota; Mayo Memorial Auditorium; 8:15 p.m.

* * *

Continuation Course

The University of Minnesota announces a continuation course in Allergy and Chest Diseases for General Physicians to be held at the Center for Continuation Study from April 18 to 20, 1955. Special emphasis will be placed on the management of commonly met problems in these fields. Skin testing methods will be demonstrated and discussed. Guest speaker will be Dr. Leslie N. Gay, Associate Professor of Medicine, Johns Hopkins University, Baltimore, Maryland, who will also deliver the annual Clarence M. Jackson Lecture on Tuesday evening, April 19. The program will be presented under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine.

* * *

Extension Course in Medical Terminology

The University of Minnesota will offer a short course on the Introduction to Anatomy and Medical Terminology on eight consecutive Friday evenings from 7:30 to 9:30 beginning tonight, Friday, April 15, in Room 100, Mayo Memorial. The course is planned for medical secretaries, social workers, medical and x-ray technicians, pharmacists, administrators, medical record librarians, and other persons using medical terms in their daily work. Instructors will be Dr. Stewart Thomson, Assistant Director of the School of Public Health, and Samuel Cornwell, who was an Assistant Director of Anatomy at the University until recently when he began studies for his doctor of medicine degree.

Registration may be made by mail or in person at: 57 Nicholson Hall, University of Minnesota; 690 Northwestern Bank Building, Minneapolis; or St. Paul Extension Center, Wabasha and College Avenues, St. Paul. Cooperating with the University's General Extension Division to present the short course are the Twin City Chapter of Medical Record Librarians; the Minnesota Hospital Association, the Minnesota Department of Health, the Minnesota State Medical Association, and the University of Minnesota Hospitals.

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(continued on next page)

Dr. Boyden Honored

Last week Dr. Edward A. Boyden was chosen President Elect of the American Association of Anatomists. The election occurred at the 68th annual session of the Anatomists, which was held from April 6 to 8 at the Jefferson Medical College, Philadelphia. Dr. Boyden will serve for three years: first as President Elect, then as President, and then as President Emeritus and member of the Executive Committee.

Dr. Boyden is Professor Emeritus of Anatomy, the Medical School, University of Minnesota, and currently is a visiting professor at the University of Washington, Seattle. His recent book, "Segmental Anatomy of the Lungs," was published in February, 1955. Dr. Boyden will attend the Sixth International Congress of Anatomy, Paris, July 25-30, 1955, where he will serve as an American member of the Committee on Nomenclature.

* * *

Faculty News

Dr. Arnold Lazarow, Professor and Head, Department of Anatomy, recently returned from Cleveland where he participated in a postgraduate course given at the Cleveland Clinic under the auspices of the American College of Physicians. He presented two lectures entitled "Experimental Diabetes" and "Principal Pathways of Intermediary Metabolism." Dr. Lazarow, along with his colleagues in the Department of Anatomy, Dr. L. J. Wells, Professor, Dr. J. F. Hartmann, Associate Professor, Dr. Richard G. Hibbs, Instructor, and Mrs. Marilyn Farquhar, Research Fellow, also attended the annual meeting of the American Association of Anatomists which was held in Philadelphia from April 6 to 8. Several members of the Anatomy Department also attended the Histochemical Society Meeting on April 4 and 5.

Dr. Dennis W. Watson, Professor of Bacteriology and Immunology, recently attended the annual meeting of the Commission on Immunization of the Armed Forces Epidemiological Board held at the Army Medical Center, Washington, D. C. Dr. Watson has been an Associate of the Commission since 1947.

Dr. W. D. Armstrong, Professor and Head, Department of Physiological Chemistry, Dr. Leon Singer, Assistant Professor, and Mr. P. Venkateswarlu, Research Fellow, attended a special conference held under the auspices of the U.S. Public Health Service on the methods of fluorine determination with particular application to blood in Evanston, Illinois, on March 21 and 22. Dr. Armstrong and Dr. Singer also attended the meeting of the International Association for Dental Research in Chicago from March 18 to 20, and Dr. Armstrong the meetings of the American Chemical Society in Cincinnati on March 31. Dr. Armstrong also participated in a special symposium on Clinical and Biological Aspects of Growth and Development of Dental and Skeletal Tissues in Boston on March 28 and 29, a symposium held under the auspices of the Forsyth Dental Infirmary for Children and the Harvard School of Dental Medicine, where he presented a paper on "Bone." Dr. W. O. Caster, Associate Professor, and Dr. Charles W. Carr, Assistant Professor, attended the meetings of the Federation of American Societies for Experimental Biology which was held in San Francisco from April 11 to 15.

Dr. Fouad A. Bashour, Medical Fellow in the Department of Medicine, left on April 1 for his native Lebanon where he will speak before the Middle East Medical Assembly to be held at the American University of Beirut from April 22 to 24. Dr. Bashour will join Dr. C. J. Watson, Professor and Head, who has been visiting Europe and the Middle East under the auspices of the State Department.

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

April 18 - 23, 1955

Monday, April 18

Medical School and University Hospitals

- 9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.
- 10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.
- 11:30 - Tumor Conference; Doctors Hitchcock, Zimmermann, and Stenstrom; Todd Amphitheater, U. H.
- 11:30 - 12:30 Physical Medicine and Rehabilitation Staff Seminar; Rehabilitation Techniques for the Newly Blind; Jeff Woodring, Minneapolis Society for the Blind; Heart Hospital Theater.
- 12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
- 1:00 - 2:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.
- 1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker, and Staff; U.H.
- 1:30 - 3:30 Dermatology Hospital Rounds; H. E. Michelson and Staff; Dermatology-Histopathology Room, C-394 Mayo Memorial.
- 4:00 - 6:00 Anesthesiology Conference; F. H. Van Bergen and Staff; Todd Amphitheater, U. H.
- 4:30 - Public Health Seminar; Issues in Social Organization of Medical Care; Franz Goldmann, Associate Professor of Medical Care, School of Public Health, Harvard University; 100 Mayo Memorial.
- 4:30 - Pediatric-Medicine Infectious Disease Rounds; Station 33, U. H.
- 5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater,

Ancker Hospital

- 8:00 - 9:00 Pediatric Contagion Rounds; Richard Lein; Contagion 5.
- 8:30 - 10:30 Medical and Surgical Chest Conference; Dr. Gehlen and Staff; Auditorium.
- 9:30 - 12:00 Visiting Staff Rounds.
- 10:00 - 12:00 Surgery Grand Rounds; Begin Floor E4.
- 11:00 - 12:00 Pediatric Rounds; Harry Orme; Contagion 1.
- 12:30 - 2:30 Surgery Out-Patient Clinic; Room 8.

Monday, April 18 (Cont.)

Ancker Hospital (Cont.)

- 2:00 - 3:00 Routine EKG Interpretation; Dr. Sommers and House Staff; Medical Record Library.
- 2:30 - 3:00 Discussion of Problem Case; Auditorium.
- 3:00 - 4:00 Surgery Journal Club; Classroom.
- 3:00 - 4:00 Lectures on Electrocardiography; Ben Sommers; Auditorium.
- 4:00 - 5:00 Medical Clerk Journal Club; Auditorium.

Minneapolis General Hospital

- 10:30 - 12:00 Medicine Rounds; Paul Lowry; Station 31.
- 10:30 - Orthopedic and Fracture Rounds; Drs. John Moe and O. J. Campbell; Station 20.
- 11:00 - Pediatric Case Discussions; Erling Platou; Station 4.
- 12:30 - Surgery Grand Rounds; O. J. Campbell, Station 21.
- 1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Station 8.
- 2:00 - Pediatric Rounds; William Krivit; Stations 4, 5, & 6.

Veterans Administration Hospital

- 9:30 - Infectious Disease Rounds; Drs. Hall, Zinnemann, and Doe.
- 1:30 - Cardiac Conference; Drs. Smith, Berman, Hoseth, Simonson, and Farquhar; Conference Room, Bldg. I; Rounds immediately following conference.

Tuesday, April 19

Medical School and University Hospitals

- 9:00 - 9:50 Roentgenology-Pediatric Conference; Samuel Feinberg, John A. Anderson and Staffs; Eustis Amphitheater, U. H.
- 12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 104 Jackson Hall.
- 12:30 - 1:30 Physiological Chemistry Seminar; Metabolism of Carcinogenic Amines; John Peters; 214 Millard Hall.
- 12:30 - Anatomy Seminar; X-ray Studies of Intracellular Mass of Plant Cells; Orville Dahl; 226 Jackson Hall.
- 12:30 - Bacteriology and Immunology Seminar; Extra-Mendelian Mechanisms: Genetic Transduction of Bacteria by Viruses. Hereditary Change by Establishment of Lysogeny in C. Diphtheriae; Richard Crowell; 214 Millard Hall.
- 3:30 - General Physiology Seminar; 323 Zoology Building.
- 3:30 - Pediatric Seminar; Ebstein's Malformation; Dr. Robinson; 1450 Mayo Memorial.
- 4:00 - 5:00 Pediatric Rounds on Wards; John A. Anderson and Staff; U. H.

Tuesday, April 19 (Cont.)

Medical School and University Hospitals (Cont.)

- 4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.
4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.
5:00 - 6:00 X-ray Conference; Presentation of Cases from Mount Sinai Hospital; Drs. Friedman, Westley, and Springer; Eustis Amphitheater, U. H.
* 8:00 p.m. Clarence M. Jackson Lectureship; "A History of the Treatment of Bronchial Asthma;" Dr. Leslie N. Gay, Associate Professor of Medicine, Johns Hopkins University, Baltimore, Maryland; Mayo Memorial Auditorium.

Ancker Hospital

- 8:00 - 9:00 Pediatric Rounds; Dale Cumming; Contagion 1.
9:00 - 10:30 Visiting Staff Rounds.
9:00 - 12:00 Practical Diagnostic Clinic; Harry Orme; Out-Patient Department.
11:00 - 12:00 Medical X-ray Conference; J. R. Aurelius; Auditorium.
2:30 - 4:00 Routine EKG Interpretations; Resident Staff.
4:00 - 5:00 Medical-Pathological Conference; W. F. Mazzitello, Auditorium.

Minneapolis General Hospital

- 9:30 - Pediatric Rounds; Elizabeth Lowry and A. Bridge; Station 5.
9:30 - 10:30 Obstetrics and Gynecology Staff Rounds; William P. Sadler and Staff; 301 Harrington Hall.
10:00 - Psychiatry Grand Rounds; R. W. Anderson, Station 3.
11:00 - 12:00 Medicine-Surgery Conference; Classroom, Station 8.
12:30 - 2:30 Dermatology Rounds on Clinic; Carl W. Laymon and Staff.
12:30 - ECG Conference; Boyd Thomes and Staff; 302 Harrington Hall.
1:00 - Tumor Clinic; Drs. Eder, Coe, and Lipschultz; Classroom.
3:30 - Pediatric-Psychiatry Rounds; Station 4.

Veterans Administration Hospital

- 7:30 - Anesthesiology Conference; Surgical Conference Room, Bldg. 43.
8:30 - Hematology Rounds; Drs. Hagen and Wexler.
8:30 - Surgery Journal Club; Conference Room, Bldg. I.
9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.
10:30 - Surgery-Tumor Conference; D. Ferguson and J. Jorgens.
1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.
1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.
2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.
4:00 - Thoracic Surgical Problems; Conference Room, Bldg. I.
5:30 - Physiology Seminar; Surgical Conference Room, Bldg. 43.

Wednesday, April 20

Medical School and University Hospitals

- 11:00 - 12:00 Pathology-Medicine-Surgery-Pediatrics Conference; Todd Amphitheater, U. H.
- *12:15 - Family Doctors' Day; Division of Neurosurgery; Hospital Dining Room.
- 1:00 - 2:00 Dermatology Clinical Seminar; F. W. Lynch; 300 North Clinic.
- 1:30 - 3:00 Pediatrics Allergy Clinic; Albert V. Stoesser and Lloyd Nelson; W-211, U. H.
- 3:30 - 4:30 Dermatology-Pharmacology Seminar; 3rd Floor Conference Room, Heart Hospital.
- 4:30 - 5:50 Dermatology-Infectious Disease Seminar; 3rd Floor, Conference Room, Heart Hospital.
- 5:00 - 6:00 Radiology Residents' Lecture; Bone Metabolism; Edmund B. Flink; Todd Amphitheater, U. H.
- 5:00 - 5:50 Urological-Pathological Conference; C. D. Creevy and Staff; A503, Mayo Memorial.
- 5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.
- 7:30 - 9:30 Dermatology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

- 8:30 - 9:30 Clinico-Pathological Conference; J. Noble; Auditorium.
- 11:00 - 12:00 Pediatric and Contagion Rounds; Harry Orme; Contagion 1.
- 11:00 - 12:00 Medicine Resident Rounds; W. F. Mazzitello.
- 3:00 - 5:00 Infectious Disease Rounds; W. W. Spink; Auditorium.

Minneapolis General Hospital

- 10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station 11.
- 11:00 - Pediatric Rounds; Erling Platou and Richard Raile; Station 6.
- 12:00 - Surgery-Physiology Conference; O. J. Campbell and E. B. Brown; Classroom.
- 12:30 - Pediatrics Staff Meeting; Classroom, Station 4.

Veterans Administration Hospital

- 8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Surgical Conference Room, Bldg. 43.
- 8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.
- 9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Ferguson, Brakel, Vennes, Nesbitt and Sadoff.
- 10:30 - Psychosomatic Conference; C. K. Aldrich; 7th Floor, Bldg. 43.
- 12:30 - Medical Journal Club; Doctors' Dining Room.

Wednesday, April 20 (Cont.)

Veterans Administration Hospital (Cont.)

- 12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.
- 1:30 - 3:00 Metabolic Disease Conference; Drs. Flink and Shapiro.
- 3:30 - Urology Pathology Slide Conference; Dr. Gleason; Conference Room, Bldg. I.
- 7:00 - Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, April 21

Medical School and University Hospitals

- 9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Room 3.148 Mayo Memorial.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom, B. Zimmermann; Todd Amphitheater, U. H.
- 12:30 - 1:55 Physiology Seminar 210; Transport; Selected Topics in Advanced Permeability; Nathan Lifson; 214 Millard Hall.
- 12:30 - 1:30 Endocrine Seminar; Regulation of ACTH Output; Dr. Royce; 271 Lyon Laboratories.
- 1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.
- 4:00 - 5:00 Anesthesiology Seminar; F. H. Van Bergen and Staff; Room 100, Mayo Memorial.
- 5:00 - 6:00 Radiology Seminar; Intravenous Cholangiography; Robert Kurth; Eustis Amphitheater, U. H.
- 7:30 - 9:30 Physiology 211 Seminar; Selected Topics in Heart and Circulation; Hemodynamics; M. B. Visscher and Robert Evans; 271 Lyon Laboratories.

Ancker Hospital

- 9:00 - 10:00 Pediatric Contagion Rounds; Alexander Stewart, Contagion 5.
- 9:30 - 10:30 Medical Grand Rounds; Auditorium; Visiting Staff Rounds immediately following Grand Rounds.
- 11:00 - 12:00 Medicine Resident Rounds; W. F. Mazzitello.
- 2:00 - 3:00 Routine ECG Interpretation; Ben Sommers; Medical Record Library.

Minneapolis General Hospital

- 9:30 - Neurology Rounds; Heinz Bruhl; Station 4.
- 9:30 - Pediatric Contagion Rounds; R. B. Raile; Station 4.
- 10:00 - Psychiatry Grand Rounds; R. W. Anderson and Staff; Station 3.
- 11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.
- 12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.
- 1:00 - Fracture X-ray Conference; Drs. Campbell and Moe; Classroom.
- 1:00 - House Staff Conference; Station 4.

Thursday, April 21 (Cont.)

Veterans Administration Hospital

- 8:00 - Experimental Surgery Laboratory Meeting; Conference Room, Bldg. I.
- 8:30 - Hematology Rounds; Drs. Hagen and Duryea.
- 9:00 - Surgery Grand Rounds; Conference Room, Bldg. I.
- 9:00 - Surgery Ward Rounds; D. Ferguson and Staff; Ward 11.
- 11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.
- 1:00 - Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I. (Rounds immediately following conference).

Friday, April 22

Medical School and University Hospitals

- 8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.
- 9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.
- 10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Eustis Amphitheater, U. H.
- 11:45 - 12:50 University of Minnesota Hospitals Medical Staff Meeting; Clinical and Experimental Investigations of a Heparin - Precipitable Fibrinogen Fraction; Richard T. Smith; Powell Hall Amphitheater.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.
- 1:00 - 2:00 Physiology Seminar 212; Selected Topics in Respiration: Respiratory and Circulatory Effects of Hypothermia; E. B. Brown; 214 Millard Hall.
- 1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Eustis Amphitheater, U. H.
- 2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatological Histopathology Room, C-394 Mayo Memorial.
- 3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.
- 3:30 - 4:30 Dermatology-Physiology Seminar; 3rd Floor Conference Room, Heart Hospital.
- 4:00 - 5:30 Chest X-ray Conference; Chest Staff and Charles Nice; Todd Amphitheater, U. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hanson and Staff; E-534, U. H.
- 5:00 - Urological Seminar and X-ray Conference; A-503, Mayo Memorial.

Ancker Hospital

- 8:00 - 9:00 Pediatric Rounds; Charles Steinberg; Contagion 1.
- 10:30 - 11:30 Pediatric Contagion Rounds; Richard Smith; Contagion 1.

Wednesday, April 20 (Cont.)

Veterans Administration Hospital (Cont.)

- 12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.
- 1:30 - 3:00 Metabolic Disease Conference; Drs. Flink and Shapiro.
- 3:30 - Urology Pathology Slide Conference; Dr. Gleason; Conference Room, Bldg. I.
- 7:00 - Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, April 21

Medical School and University Hospitals

- 9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Room 3.148 Mayo Memorial.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom, B. Zimmermann; Todd Amphitheater, U. H.
- 12:30 - 1:55 Physiology Seminar 210; Transport; Selected Topics in Advanced Permeability; Nathan Lifson; 214 Millard Hall.
- 12:30 - 1:30 Endocrine Seminar; Regulation of ACTH Output; Dr. Royce; 271 Lyon Laboratories.
- 1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.
- 4:00 - 5:00 Anesthesiology Seminar; F. H. Van Bergen and Staff; Room 100, Mayo Memorial.
- 5:00 - 6:00 Radiology Seminar; Intravenous Cholangiography; Robert Kurth; Eustis Amphitheater, U. H.
- 7:30 - 9:30 Physiology 211 Seminar; Selected Topics in Heart and Circulation; Hemodynamics; M. B. Visscher and Robert Evans; 271 Lyon Laboratories.

Ancker Hospital

- 9:00 - 10:00 Pediatric Contagion Rounds; Alexander Stewart, Contagion 5.
- 9:30 - 10:30 Medical Grand Rounds; Auditorium; Visiting Staff Rounds immediately following Grand Rounds.
- 11:00 - 12:00 Medicine Resident Rounds; W. F. Mazzitello.
- 2:00 - 3:00 Routine ECG Interpretation; Ben Sommers; Medical Record Library.

Minneapolis General Hospital

- 9:30 - Neurology Rounds; Heinz Bruhl; Station 4.
- 9:30 - Pediatric Contagion Rounds; R. B. Raile; Station 4.
- 10:00 - Psychiatry Grand Rounds; R. W. Anderson and Staff; Station 3.
- 11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.
- 12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.
- 1:00 - Fracture X-ray Conference; Drs. Campbell and Moe; Classroom.
- 1:00 - House Staff Conference; Station 4.

Thursday, April 21 (Cont.)

Veterans Administration Hospital

- 8:00 - Experimental Surgery Laboratory Meeting; Conference Room, Bldg. I.
- 8:30 - Hematology Rounds; Drs. Hagen and Duryea.
- 9:00 - Surgery Grand Rounds; Conference Room, Bldg. I.
- 9:00 - Surgery Ward Rounds; D. Ferguson and Staff; Ward 11.
- 11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.
- 1:00 - Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I. (Rounds immediately following conference).

Friday, April 22

Medical School and University Hospitals

- 8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.
- 9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.
- 10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Eustis Amphitheater, U. H.
- 11:45 - 12:50 University of Minnesota Hospitals Medical Staff Meeting; Clinical and Experimental Investigations of a Heparin - Precipitable Fibrinogen Fraction; Richard T. Smith; Powell Hall Amphitheater.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.
- 1:00 - 2:00 Physiology Seminar 212; Selected Topics in Respiration: Respiratory and Circulatory Effects of Hypothermia; E. B. Brown; 214 Millard Hall.
- 1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Eustis Amphitheater, U. H.
- 2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatological Histopathology Room, C-394 Mayo Memorial.
- 3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.
- 3:30 - 4:30 Dermatology-Physiology Seminar; 3rd Floor Conference Room, Heart Hospital.
- 4:00 - 5:30 Chest X-ray Conference; Chest Staff and Charles Nice; Todd Amphitheater, U. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hanson and Staff; E-534, U. H.
- 5:00 - Urological Seminar and X-ray Conference; A-503, Mayo Memorial.

Ancker Hospital

- 8:00 - 9:00 Pediatric Rounds; Charles Steinberg; Contagion 1.
- 10:30 - 11:30 Pediatric Contagion Rounds; Richard Smith; Contagion 1.

Friday, April 22 (Cont.)

Ancker Hospital (Cont.)

- 11:00 - 12:00 Contagion Rounds; Harry Orme; Contagion 5.
- 2:00 - 3:00 Routine EKG Interpretation; Resident Staff.
- 3:00 - 4:00 Medical-Surgical-Pathological Conference; Auditorium.
- 4:00 - 5:00 Medical Journal Club; Conference Room, E5.
- 4:00 - 5:00 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

- 10:00 - Otolaryngology Conference; Robert A. Priest, Large Classroom.
- 10:30 - Pediatric Surgical Conference; Tague Chisholm and B. Spencer; Classroom, Station 4.
- 12:00 - Surgery-Pathology Conference; Drs. Campbell and Coe; Classroom.
- 1:00 - 3:00 Clinical-Medical Conference; Thomas Lowry; Classroom, Station 8.

Veterans Administration Hospital

- 10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.
- 11:00 - 12:30 Psychiatry Case Conference; Werner Simon; Psychiatry Department, VA Hospital Annex.
- 12:30 - Urology X-ray Conference; X-ray Department.
- 1:00 - CPC Conference; Conference Room, Bldg. I.
- 2:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

Saturday, April 23

Medical School and University Hospitals

- 7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.
- 9:00 - 9:30 Pediatric Grand Rounds; Eustis Amphitheater, U. H.
- 9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.
- 9:15 - 10:00 Surgery-Roentgenology Conference; Alexander R. Margulis, Owen H. Wangenstein and Staff; Todd Amphitheater, U. H.
- 10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.
- 10:00 - 12:50 Obstetrics and Gynecology Rounds; J. L. McKelvey and Staff; Station 44, U. H.
- 10:00 - 12:00 Otolaryngology Seminar on Current Literature; L. R. Boies and Staff; Todd Memorial Room, A-675, Mayo Memorial.
- *11:00 - Special Radiology Seminar; Roentgenologic Aspects of Some Sclerosing Lesions of Bone; Dr. Lester W. Paul, Professor of Radiology, University of Wisconsin; Eustis Amphitheater, U. H.

Saturday, April 23, (Cont.)

Ancker Hospital

- 8:30 - 9:30 Surgery Conference, Auditorium.
- 9:30 - 11:00 Medicine Grand Ward Rounds; W. F. Mazzitello.
- 11:00 - 12:00 Medical Clerk Case Conference; W. F. Mazzitello.

Minneapolis General Hospital

- 8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.
- 9:00 - Psychiatry Grand Rounds; R. W. Anderson; Station 3.
- 9:30 - Pediatrics Rounds on all Stations; R. B. Raile.
- 11:00 - 12:00 Medical X-ray Conference; O. Lipschultz, Thomas Lowry and Staff; Main Classroom.

Veterans Administration Hospital

- 8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.
- 8:30 - Medical X-ray Conference; Conference Room, Bldg. I.

* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.