CANCER CLINIC

Combined Medical Radiotherapy
Clinical Conference

Conducted by J. J. Nickson, M.D., and A. S. Glicksman, M.D.

For the past three and one-half years it has been the practice at Memorial Center to have a medical consultant in the Department of Radiotherapy. An attending radiotherapist and the medical consultant jointly conduct rounds daily on all ward patients who are immediately under the care of the Radiotherapy Department, that is, assigned to one of their ward beds. The radiotherapy residents are required to attend these rounds twice a week.

Approximately two thirds of the patients admitted to James Ewing Hospital...
with a diagnosis of cancer have an associated medical problem. A recent study on 950 consecutive admissions revealed that one third of the patients with malignant neoplasms had either overt diabetes or an aberration in carbohydrate metabolism. In a publication last year (see p. 147), this group discussed the common electrolyte disturbances in patients undergoing radiotherapy. It is the purpose of this conference to demonstrate three typical medicoradiotherapeutic problems that are to be found on this service at present.

Case I. Mrs. R. K., a 44-year-old white female, was admitted to the radiotherapy service of the James Ewing Hospital on June 30, 1958 complaining of abdominal cramps, nausea, anorexia, marked lethargy, weakness and headache. Four and a half years ago the patient had a radical mastectomy for carcinoma of the right breast. No postoperative radiation therapy was given. A year and a half ago, the patient developed recurrences on the anterior chest wall and skeletal metastases and was advised to have a bilateral oophorectomy which was performed on January 1, 1957. Remission lasted nine months. With the recrudescence of the disease, meticorten therapy was instituted. This appeared to produce another remission and in January, 1958 a bilateral adrenalectomy was performed. At that time the surgeons reported liver metastases seen through the peritoneum. Following the adrenalectomy, the patient was maintained on 75 mg. of cortisone daily by mouth. Two weeks prior to admission the patient was referred to the radiotherapy service for a course of radiation to the persistent, progressive disease in the anterior chest wall. The patient was started on betatron therapy with electron beam to the chest wall, to an area containing several skin metastases, the largest measuring 8 x 6 cm. A 15 x 15 cm. portal was used with an energy of 10.4 mev.

Dr. Nickson: The electron beam was chosen since by its use the underlying pulmonary and mediastinal structures would be spared. The electron beam differs qualitatively from X-ray beams in that the energy is not exponentially absorbed within the tissues but rather has a definite range. Thus only 10 per cent of the maximal energy was found at a depth of 5 cm. from the surface. The use of electron beams thus eliminates the complication of pulmonary fibrosis seen after X-ray treatment for similar conditions.

Dr. Glicksman: Approximately four days prior to admission the patient felt rather weak; she lost her appetite and vomited on occasion. She did not recall whether the cortisone tablets which she took regularly were retained or regurgitated. Because of the progressive weakness, nausea, vomiting and abdominal cramps, the patient was admitted for evaluation and to continue her therapy as an in-patient. On admission, physical examination revealed a well developed, well nourished white female who appeared acutely ill. Blood pressure was 88/60, pulse 120, weak and thready, respirations, 24, and deep. The pertinent physical findings included the absence of the right breast and the presence of metastatic nodules on the anterior chest wall covering an area of 5 x 4 cm. The heart and lungs were normal, the liver was palpable one finger below the costal margin. There were no significant masses in the abdomen, there was a generalized diffuse tenderness but no specific area of intense pain, localization or rebound. The rectal and vaginal examinations were essentially negative. Neurological examination revealed a diminution in the deep tendon reflexes throughout. No pathologic reflexes were elicited. The pertinent laboratory determinations are given in Table I.

| Date    | BUN | Na  | K  | Cl | CO₂ | Hb  | Hct |
|---------|-----|-----|----|----|-----|-----|-----|
| 6/25/58 | 25.5| 136 | 5.87| 96 | 20  | 15.5| 47  |
| 6/27/58 | 20.0| 134 | 5.30| 102| 24  | 14.0| 43  |
| 7/7/58  | 15.4| 135 | 5.31| 101| 24  | 13.8| 42  |

Resident: This is a typical picture of adrenal insufficiency. Is adrenal insufficiency a common complication of radiation therapy?

Dr. Glicksman: This patient represents a fairly typical case of adrenal insufficiency.
When the radiotherapy was instituted the patient was placed under additional stress; however, since her own adrenals had been removed and she was completely dependent upon exogenous adrenocortical hormone she could not meet the additional demand, therefore she developed a relatively severe adrenal insufficiency. The clinical picture of marked weakness and gastrointestinal complaints is fairly characteristic of the syndrome and is seen in 90 per cent of the cases. The serum electrolytes adequately demonstrate the metabolic acidosis which develops in these cases. The low sodium and relatively high potassium are characteristic of the syndrome and occur because of an increased Na and Cl excretion and K retention. The slightly elevated blood urea nitrogen reflects a decrease in the glomerular filtration rate associated with the usual hemococoncentration of these patients.

This patient was started on replacement therapy intravenously and received 100 mg. of intravenous cortisone (solucortef) in 5 per cent glucose and saline. Within six hours after the infusion the patient felt considerably stronger, and nausea, vomiting and abdominal cramps had subsided. Her blood pressure rose to 110/80, pulse dropped to 100. Her hematocrit reading, however, fell only to 43. She was started on intramuscular injections of cortisone (150 mg. per day) but the intravenous cortisone and saline were continued. The patient was continued on intramuscular cortisone for approximately one week and then given 125 mg. by mouth until the completion of radiation therapy. Upon the completion of radiation therapy the cortisone was slowly decreased to her usual maintenance dose of 75 mg. per day.

The patient made an uneventful recovery and continued her radiotherapy. Twenty-four treatments were given in forty days to a total tumor dose of 5200 r. There was good response in terms of diminution of the ulcerated areas.

**RESIDENT:** Do you see many cases here of adrenal insufficiency owing to stress of therapy?

**DR. GLICKSMAN:** This is not an unusual or uncommon complication. We had the opportunity in the last three and a half years to observe approximately six such cases and an additional nine cases of adrenal exhaustion in breast cancer patients who had not had adrenalectomies. The important point is that radiation therapy adds an additional stress to the patient. Should the patient be an adrenalectomized or hypophysectomized patient increased maintenance dosage of cortisone is indicated.

In the other large group of patients who developed the syndrome, are those patients who have been subjected to surgical procedures, to bone pain from metastatic disease or to additional emotional stresses placed upon them by the realization of the nature of their illness. When radiotherapy is instituted these patients may not have adequate adrenal function to withstand the additional demands and may develop relative adrenal exhaustion. They must be started on exogenous cortisone if adequate radiation therapy is to be carried to the completion of the prescribed course.

**RESIDENT:** Do you feel that postoperative radiation therapy has proved worthwhile?

**DR. NICKSON:** The question of the "worthwhileness" of postoperative radiation therapy to the site of operation and regional nodes after radical mastectomy remains a puzzling one. Neilson's series, reported just after the war, indicated a slightly, but statistically significant, increased survival in those patients receiving postoperative irradiation over those not so treated. Many of the earlier and negative studies were associated with low doses to the chest wall and to the regional nodes, doses of the order of 1500 to 2000 r. A properly planned series, preferably with random assignment of patients to the radiation and nonradiation group with doses ranging around 4000 r to the regional nodes, needs to be studied before any definitive answer can be given to the value of routine postoperative radiation treatment. It seems to me that in institutions where the incidence of chest-wall recurrence is less than 15 per cent, little is to be gained by treatment of the chest wall. On the other hand, treatment of the regional
nodes usually deemed inaccessible, the internal mammary and the supraclavicular nodes, probably is worthwhile. The dose must be as large as possible to give maximal chance for arresting any cancer cells in these areas. Doses of the order of 4000 r to the supraclavicular nodes and to the internal mammary nodes in three and a half to four weeks would appear to be optimal and feasible at this time. The major question, of course, remains. If these regional nodes are involved, what is the likelihood that the disease has not already spread to other areas in the body? No firm answer can be given to this question. It would appear that only by doing a properly designed clinical investigation would it be possible to derive a practical answer.

RESIDENT: Do you think that conventional radical mastectomy will be superceded by simple mastectomy plus postoperative radiation?

DR. NICKSON: The relative merits of routine radical mastectomy for patients with primary carcinoma of the breast versus simple mastectomy and postmastectomy radiation of the contents of the axillary, supraclavicular and internal mammary spaces remain an active and stimulating question. There is no gainsaying the fact that the five- and ten-year survivals reported by McWhirter, using simple mastectomy plus radiation, compare very favorably with those reported from good centers relying primarily on radical mastectomy. There are great difficulties in analyzing these figures since the clinical classifications used in varying centers differ enough to make it uncertain that one is comparing like types of cases. Nevertheless, the over-all absolute survival of patients treated by the newer procedure appeared to be as good as, and possibly in some instances better than, that achieved with radical mastectomy.

It is not my view that an institution which today has the radical mastectomy well in hand should depart from this procedure unless it also has an active and competent department of radiology with a broad spectrum of equipment. The problem is one for the clinical investigative centers to resolve and not one for the practitioner to adopt. It is not my feeling that standard and useful means of treatment of cancer should be abandoned until it is well established that the supplanting procedure is better than the older one.

Case 2. Mrs. A. K., a 47-year-old white female, was first seen at this institution approximately four months ago with a large fungating mass in the left breast. Two 3-cm. nodes were palpable in the axilla. Prior to admission to the hospital the patient was carefully evaluated as to her operability. A skeletal survey failed to reveal any bone metastases. Chest plate was within normal limits. Serum calcium and urinary calcium were normal. Serum alkaline phosphatase and BSP were similarly normal. Therefore, in May, 1958 a left radical mastectomy was performed. Nodes were positive at all levels. The patient made an uneventful recovery from the surgical procedure. However, four weeks following discharge from the hospital the patient was seen in the clinic complaining of headache, lethargy and double vision. Neurological consultation and lumbar puncture substantiated the clinical impression of intracranial metastases. Radiotherapy consultation was requested; after the patient was started on radiation therapy to the head she was transferred to the radiotherapy service. On admission to this service the significant physical findings included nystagmus, papilledema, a well healed left mastectomy scar, normal heart and lungs. The abdomen was flat and soft, the liver was palpable two fingers below the costal margin and tender. No other intra-abdominal mass or organomegaly was palpable. She still had adiadochokinesis and astereognosis. There were no sensory or reflex changes. Significant laboratory findings included: Blood urea nitrogen of 10 mg./100 ml.; bilirubin 1.2 mg./100 ml., BSP 47 per cent, alkaline phosphatase 12 units/100 ml., cephalin flocculation 2+, thymol turbidity 3.4 units, the prothrombin time was 15.8 seconds; total protein (gm./100 ml.) 7.5, albumin 4.2 gm., globulins 3.4, CO₂ was 18, chloride 100, sodium 134, potassium 5.1 mEq./L.
DR. NICKSON: The use of radiation for treatment of secondary intracranial involvement deserves some comment here. Over the past five to six years the department has explored the role of treatment of patients with neurological defects. We have come to the conclusion that routine irradiation of these patients is a worthwhile palliative measure. A favorable response is seen in approximately one half of these patients as judged by decrease in their neurological defects or return to a normal neurological status. The duration of this improvement is, of course, variable. The maximum recorded duration of improvement is 24 months. The minimum that we feel may be regarded as justifying treatment is four months. Another factor influencing decision to treat deserves mention. Many of these patients by virtue of their neurologic metastases are incontinent of urine and feces, and otherwise incapable of managing themselves. This then places a severe burden upon family, patient and society. Good palliation then relieves a threefold burden and converts a patient whose care is expensive to a patient who can usually manage by himself at home.

The neurologic examination prior to initiating treatment showed paresis of the third, fourth and sixth cranial nerves. Headache and diplopia were the chief complaints. Upon completion of treatment, headache had diminished but diplopia was still present. This is not uncommon since improvement of some, on occasion all, neurologic signs or symptoms occurs after completion of treatment. This is a very interesting and unusual case. The rapidity of onset of evidence of metastatic disease after a careful screening before the surgical procedure, makes one believe that this woman has a very aggressive tumor. While this is somewhat unusual, it does however fall within the normal characteristics for this disease.

RESIDENT: In retrospect, considering rapid onset of symptoms of metastatic disease following the operation, would it have been preferable not to have intervened surgically?

DR. Glicksman: It is of some interest that some patients appear to live in equilibrium with their tumors, while in other patients the tumors appear to grow in an uncontrollable fashion. One cannot help but consider the possibility that there may be another group of people who have a natural mechanism to control their tumors to the point of making treatment unnecessary. If one understood the natural mechanisms in those patients who can control their own tumors it might prove of tremendous therapeutic importance.

This tumor-host relationship can be affected by various regimens, the fundamental aim of which would be to improve the patient's ability to handle the tumor. Thus, surgical excision attempts to remove the tumor, thereby making it unnecessary for the patient to handle the disease at all: radiotherapy attempts to destroy the neoplastic tissue. Chemotherapy similarly attempts to interfere with the metabolism of the tumor in such a way that it would be destroyed. Upon occasion any of these therapeutic modalities may shift the tumor-host relationship, not in favor of the patient, but rather in favor of the tumor. Thus very shortly after surgical intervention widespread metastases may become apparent. Similarly, following radiation therapy an occasional patient may develop recurrent disease solely in the area of prior irradiation. This may be the situation in this patient where the tumor-host relationship was altered in favor of the tumor.

RESIDENT: Must one assume that changes in hepatic function are due to metastatic disease?

DR. Glicksman: One cannot assume that the liver pathology is absolutely due to metastatic disease, but, of course, this would be our first choice. However, other possibilities must be considered. This woman has been operated upon within the last three months. She has also had injections of various antibiotics and analgesics; she had two transfusions two months ago. The time element is just about right for hepatitis, i.e., homologous serum jaundice. Furthermore, one cannot overlook the
possibility that the patient was given a drug for her nausea and vomiting by her local physician which may prove to be hepatotoxic such as the chlorpromazine group of drugs. A further possibility is that the woman came in contact with infectious hepatitis. Before instituting definitive therapy for control of metastatic disease in the liver, it is therefore of primary importance to be certain of the diagnosis. There have not been any clear-cut studies to indicate that radiotherapy delivered to an infected liver would worsen the disease; but intuitively one would have to assume it would not do very much good, if indeed it did not cause some harm. On the other hand, if the liver disease were neoplastic in origin, a course of radiotherapy to the liver may prove of some palliative benefit.

The serum glutamic oxaloacetic transaminase (SGOT) level would be of great help in the differential diagnosis. In homologous serum jaundice as well as viral hepatitis (catarrhal jaundice), SGOT will be markedly elevated (sometimes as high as 5000). The serum pyruvic oxaloacetic transaminase and lactic acid dehydrogenase level, will similarly be elevated. These enzyme levels are only slightly elevated in metastatic disease to the liver. Another diagnostic aid would be a liver aspiration. Provided that the prothrombin, bleeding and clotting times are normal and an adequate platelet count is present this procedure can be done with relatively little risk to the patient. The morbidity and mortality rate for aspiration biopsy of the liver is less than 1/10th of 1 per cent. Considering the importance of the information this is a negligible risk that should be undertaken wherever feasible.

DR. NICKSON: The question of palliation of secondary metastases in the liver has also received attention over the past five or six years. A detailed account of our experiences is not possible here. It can be summarized by saying that where pain, nausea and vomiting are the dominant symptoms they can be relieved with 75 per cent probability by the use of radiation. Commonly we employ 2500 to 3000 r to the entire liver with 1 mev X-ray beam in about two weeks. Concomitant with the improvement in symptoms, improvement in some or all of the liver function studies may be seen. Duration of improvement is short and for this reason we do not advocate routine treatment of patients with hepatic metastases. However, for those patients in whom the involvement of this organ by cancer is incapacitating, treatment may be indicated.

Case 3. Mrs. E. P., a 46-year-old colored female, was seen for the first time at Memorial Center in February, 1958, at which time a carcinoma of the cervical stump was found. The patient was treated by intracavitary radium and external ionizing radiation. There was initial improvement in the findings on serial pelvic examination and on serial Papanicolaou study.

DR. NICKSON: The management of this condition radiologically is hampered by the lack of the body of the uterus as a holder for radium. This limits the value of intracavitary radium. The radiologist must place greater reliance upon his external treatment with X-ray beams. Commonly, it is not possible to deliver more than 4000 or 5000 r to point A with intracavitary sources, and this only if a small tandem can be inserted into the cervical canal. Since greater reliance has to be placed on the external treatment we prefer to give external treatment with supervoltage X-ray or gamma-ray beams, including the entire pelvis and posterior opposing fields rather than to use divided field techniques. Dose should be carried as high as possible, but seldom should the mid-plane dose for the external treatment be less than 5000 r. This, commonly, cannot be delivered in less than five weeks. In patients whose side effects are severe, the time must be increased. By utilizing careful radiologic management and by individualizing treatment to the patient's circumstance, survival figures have been reported which compare favorably with those for carcinoma of the cervix in the undisturbed pelvis.

RESIDENT: At her last clinic appearance the patient complained of headache, puffiness of the face, nausea, anorexia and an-
uria of 36 hours' duration. Pertinent physical findings included blood pressure 210/120, 2+ papilledema, marked periorbital swelling, distended neck vessels, wet bilateral rales, heart enlarged to the left with a soft, systolic, apical murmur, liver palpable one finger below the costal margin. There was a grapefruit sized mass in the lower center abdomen. On pelvic examination there was a stony hard, fixed mass which was filling the pelvis and extended above the pelvic brim. There was 2+ pitting edema of the lower extremities. Hyperreflexia was also present. Catheterization yielded no urine.

The amount of fluid that was replaced was two thirds of the total loss. The BUN came down to normal within a week postoperatively.

Dr. Nickson: The whole question of treatment of recurrent carcinoma of the cervix is currently being reevaluated. The old position that these patients could not be helped following a definitive course of either surgery or radiation is probably not true. Our experience with patients recurrent after surgery would indicate that in a small selected group of patients, those with central recurrence unattached to the pelvic wall have a good chance of palliation or survival indefinitely, without reappearance of carcinoma of the cervix.

Some patients have survived from three to five years after proved surgical recurrence. The question of re-irradiation of radiation recurrence has been investigated by Murphy's group at the Roswell Park Memorial Hospital. In a similar class of patients, he has been able to show that re-irradiation does produce a small though definite probability of indefinite freedom from disease.

Brunschwig's study at Memorial Hospital has shown that operative procedures for carcinoma, recurrent after radiation or surgery provided that the lesion is centrally located, also have a good chance of palliation. Thus we see that thoughtful application of good surgical or good radiological techniques in selected patients has a good chance of palliation or even a small chance of cure, accepting the usual definitions of this term.

Medicine today is a fine mixture of art and science. No one individual can familiarize himself adequately with all the therapeutic disciplines necessary to treat adequately all patients. However, by the team work of individuals trained in the various disciplines in the management of each patient, it is possible within the scope of our present knowledge and abilities to give each patient the best of care. The cross pollination which occurs in these joint medical radiotherapy rounds, furthermore, serves a very useful purpose in the postgraduate education of our radiotherapy residents.

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**Table II**

| Date     | BUN | Na  | K  | Cl | CO₂ | pH | pCO₂ |
|----------|-----|-----|----|----|-----|----|------|
| 4/2/58   | 15  | 145 | 4.43 | 106 | 25  |
| 6/13/58  | 117 | 142 | 7.06 | 106 | 12  | 7.35| 25   |
| 6/15/58  | 67  | 142 | 6.11 | 105 | 16  |
| 6/19/58  | 31.2| 136 | 4.85 | 97  | 24  | 7.41| 42   |

Dr. Glucksman: This woman was obviously suffering from renal shutdown with renal acidosis. Although there was a slight possibility that this was due to a medical cause, e.g., chronic glomerulonephritis, lower nephron nephrosis or mercurial poisoning, the overwhelming evidence would favor ureteral obstruction because of tumor growth. Therefore, surgical consultation was requested for consideration of nephrostomy. Ureteral catheterization revealed bilateral obstruction. The patient was prepared medically by digitalization with 1.2 mg. of cedilanid intravenously. She was given 2000 cc. of 10 per cent invert sugar in water with 88 milliequivalents of sodium bicarbonate before operation.

After nephrostomy the patient required little intravenous alimentation because she could start eating almost immediately. Her appetite was good with little nausea and vomiting. In the first 48 hours following nephrostomy, the patient excreted between 3000 and 4000 cc. of urine per day. There was also a tremendous loss of electrolytes since the kidney had been damaged by the back pressure and could not retain salts, which it otherwise would be able to do. Thus in the immediate postoperative period, it was necessary to replace sodium bicarbonate and potassium.