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Current Aspects of Cancer Chemotherapy *

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John Foley, M.D.,‖ and Ignacio Fortuny, M.D.**

The past fifteen years has been an era in which cancer chemotherapy has become a third resource—along with surgical and radiological methods—in the treatment of malignant disease. Surgery and irradiation therapy selectively employed have permitted control of many cancers. The inadequacies of these therapies, however, are evident in the large number of patients with recurrences of cancer following these procedures and in the fact that in some patients these therapies cannot be carried out initially. The failure to “cure” most cancers is demonstrated by the lack of significant declines in mortality rates from cancer.

The use of chemical agents in the treatment of cancer has afforded a new means of controlling advanced or inoperable malignant lesions. The proven effectiveness of many of these agents has already established the significance of this mode of therapy. In some instances chemotherapeutic agents are preferable to the surgical or radiological therapies generally used in the past. The very rapid development of new chemotherapeutic agents has produced confusion about the selection of the most efficacious agents and the proper sequence of use. This paper will describe some of the antineoplastic agents available, especially those of specific proven value, and

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will report clinical investigations of the newer of such agents.

**Criteria of Evaluation of Tumor Response**

The evaluation of chemotherapeutic agents in the past has been handicapped by the lack of concise measurements of the anti-tumor effects. Subjective improvement cannot be employed as a measure of such effects. During the last few years, objective criteria have been established, which include the following: disappearance or decrease in size (of at least 50 per cent) of palpable tumor masses, lymph nodes, or skin nodules; healing of tumor ulcers, disappearance or decrease in size of pulmonary metastases; recalcification of osteolytic metastases; and decrease in size of the liver with concurrent improvement of liver function test results. Regression of some lesions with concomitant progression of others cannot be regarded as improvement. In leukemia a return of white blood cell count to near normal levels, a reduction in the number of abnormal cell forms, and restoration of hemoglobin to normal levels are demanded as criteria of improvement. The strict adherence to such criteria will allow careful evaluation of agents and comparison of one with another.

The duration of effectiveness is an important factor. Many agents are able to produce fleeting decreases in size of tumor masses for a few days or weeks, but a temporary shrinkage of tumor masses for less than two months cannot be regarded as a significant tumor regression. This kind of tumor shrinkage, in fact, is frequently associated with severe toxic drug reactions. It often appears that in obtaining a favorable tumor response, one must expect considerable damage to normal rapidly proliferating cells. While the gastrointestinal tract and bone marrow are primarily affected, changes in nails and hair growth may also occur. Fleeting changes do indicate an antineoplastic action of the drug used, but they are to be distinguished from significant objective responses of greater than two months duration.

Many newer agents have been administered in doses of maximum tolerance. The early development of toxic side effects has provided a simple guide for determining this sublethal dose. Exposing patients to such a high degree of toxicity has caused fleeting tumor regressions, especially of solid tumors. The lack of an accurate measure of equivalent doses among drugs has a variable effect on comparative evaluation of multiple chemotherapeutic agents. To this are added the biological variability within tumors of the same type, and the variability of stages of the disease at the point when therapy is undertaken. Standardization of these variables is not yet complete.
Chemotherapeutic agents may be divided into six categories: 1) polyfunctional alkylating agents (nitrogen mustards), 2) metabolite antagonists, 3) antibiotics, 4) hormones, 5) miscellaneous carcinostatic agents, and 6) radioactive isotopes. We will not review every agent in each of the listed types. Many have been or are currently being tested for antitumor effects. Though they have demonstrated the ability to shrink tumors, many will not prove to be of clinical value.

I. Polyfunctional Alkylating Agents

Chemicals in this class have two or more reactive groups and are able to introduce alkyl groups into various materials. The reactive alkylating groups differ in structure, solubility, and reactivity. Innumerable types of groups have been attached to produce differences in chemical properties and pharmacologic effects. Deoxyribonucleic acid (DNA) of the cell appears most vulnerable to attack. Effective agents injure rapidly proliferating cells. The regulation of dosage determines the subsequent toxic effects.

A. Nitrogen Mustards

1. Nitrogen mustard; (HN₂, Mustargen,® mechlorethamine.) Methyl-bis (β-chloroethyl) amine.
2. Uracil mustard; (U-8344) 5-bis-(2-chloroethyl)-aminouracil
3. L-phenylalanine mustard; (PAM, Melphalan,® CB-3025) p-di(2-chloroethyl)-amino-L-phenylalanine
4. DL-phenylalanine mustard; (Sarcolysin)® 3-[p-[Bis(2'-chloroethyl)amino]phenyl]-L-alanine
5. Hemi-sulfur mustard 2-chloro-2'-hydroxydiethyl sulfide
6. Chloroquine mustard
7. Nitromin Methyl-bis-(B-chloroethyl)-amine-N-oxide
8. Mannitol mustard; (BCM, Degranol) 1,6-di-[2'-chloroethylamino]-1,6-deoxy-D-mannitol di-hydrochloride
9. Tetramin
10. Chlorambucil; (Leukeran,® CB1348) p-(di-2-chloroethylamino)-phenylbutyric acid
11. Aminochlorambucil; (CB1385) [p-NN-Di-(2-chloroethyl)aminophenyl]-a-aminobutyric acid
THE MEDICAL BULLETIN

12. Cyclophosphamide; (Cytoxan®, Endoxan)
   N. N-bis(2-chloroethyl) N'-o-porpylene phosphoric
   ester diamide

B. Ethylenimines
1. Triethylene melamine; (TEM)
   2,4,6-triethylenimino-s-triazine
2. Triethylene phosphoramid (TEPA)
3. Triethylene thiophosphoramidine; (TSPA, Thio-TEPA)
   N,N,N'-triethylene thiophosphoramidine
4. E-39
   2, 5-di-prophyloxy-3, 6-di-ethyleniminobenzoquinone

C. Epoxides
1. Diepoxypiperazine

D. Sulfonic Acid Esters
1. Busulfan; (GT41, Myleran®)
   1,4-dimethanesulfonyloxybutane

II. Anti-Metabolites

A metabolite antagonist is a compound that interferes with
utilization, formation, or function of an essential metabolite by
virtue of its close structural similarity to the metabolite.

A. Folic Acid Antagonists
1. Amethopterin; (Methotrexate®)
   4-amino-N¹ methylpteroylglutamic acid
2. Aminopterin
   4-amino-pteroylglutamic acid

B. Purine Analogs
1. 6-mercaptopurine; (Purinethol®)
2. 6-methylmercaptopurine
3. 6-mercaptopurine riboside
4. 8-azaguanine
5. 6-thioguanine
6. 6-chloropurine

C. Pyrimidine Analogs
1. 6-azauracil
2. 5-fluorouracil; (FU)
3. 5-fluorodeoxyuridine; (FUDR)

D. Glutamine Analogs
1. Azaserine
   o-diazoacetyl-L-serine
2. DON
   6-diazo-5-oxo-L-norleucine

E. Nicotinamide Antagonists
1. 6-aminonicotinamide
III. Antibiotics

Actinomycin C  Mitomycin C
Actinomycin D  Mithramycin; (PA144)
Actinomycin F  Carzinophilin
Actinomycin P2  Streptonigrin
Duazomycin A  Streptovitacin A

IV. Hormones

A. Androgenic Hormones
   1. Testosterone propionate (i.m.)
   2. Fluoxymesterone (oral)
B. Estrogenic Hormones
   1. Diethylstilbestrol
   2. Sodium estrone sulfate; (Premarin®)
   3. Ethinyl estradiol
C. Adrenal Steroids
   1. Cortisone
   2. Hydrocortisone
   3. Synthetic glucocorticoids
D. Pituitary Hormones
   1. Adrenocorticotropic hormones; (ACTH)
E. Progestational Hormones
   1. Progesterone
   2. 17-alpha-hydroxyprogesterone caproate

V. Miscellaneous Carcinostatic Drugs

A. Urethane
   Ethyl carbamate
B. Colchicine Derivatives
   1. Demecolcin (Colcemid®)
      desacetylmethylcolchicine
C. Analog of DDT
   o,p'DDD (2,2-Bis[4-chlorophenyl, 2-chlorophenyl]-1, 1- Dichloroethane)
D. Hydrazones
   Nitrofurazone; (Furacin®)
E. 3-Methylcholanthrene
F. Natural products
   1. Vinblastine sulfate; (Vincaleukoblastine, Velban®)

VI. Radioactive Isotopes

A. Phosphorus (P32)
B. Iodine ($^{131}$I)
C. Gold ($^{198}$Au)

**Currently Useful Drugs**

Many agents now available have proved to be of value in the treatment of specific malignant tumors:

1) *Nitrogen mustard*, one of the oldest agents, remains valuable. Its favorable effects in stage III lymphomas and chronic leukemias are well known. It has been helpful in the acute phase of oat-cell carcinoma of the lung and in controlling effusions from malignant lesions. Remission of solid tumors has been sporadic. The inconvenience of intravenous administration, the attendant nausea and vomiting, and the depression of bone marrow function have all limited widespread use of this agent. Though similar effects occur with newer agents, use of these agents has been more intensive. The chief difficulty with nitrogen mustard has been the lack of a simple method for determining the maximum tolerated dose. Although four daily doses of 0.1 mg/Kg have been recommended, this dose in many instances is inadequate to produce anti-tumor effect. Some patients may tolerate as many as eight consecutive daily doses. Nor is the single shot of 0.4 mg/Kg an adequate dose. With careful blood determinations the maximum tolerated dose leading to a white blood count of 500 to 1000 per cu. mm. in two or three weeks can be attained. The newer cytotoxic agents permit easy determination of a dose that will produce this degree of leukopenia without exceeding the sublethal level. Presumably, if sufficiently high doses of nitrogen mustard were administered to produce gastrointestinal damage or alopecia, remissions of solid tumors would also occur. Nitrogen mustard and the L-phenylalanine derivative have been employed in perfusion studies. This technique has limited value, primarily for lesions of the extremities.

2) *Uracil mustard*: (see below)

3) *Chlorambucil*: This is an effective oral alkylating agent for the treatment of chronic lymphatic leukemia. Its ease of administration, consistent absorption, relatively slow production of toxicity, and anti-tumor activity have made it useful. The depressive effect on the bone marrow can easily be controlled. Attempts to employ this agent in the treatment of solid tumors have not been successful, since the dose required produces severe bone marrow depression. Though it is also effective in lymphomas and chronic myeloid leukemia, other agents offer more advantages.
4) Cyclophosphamide: (see below)

5) Triethylene thiophosphoramide: The effect of this compound on lymphomas is less dramatic than is that of nitrogen mustard. It also has anti-tumor properties for some solid tumors. The doses required, however, frequently result in severe bone marrow depression that is prolonged and sometimes irreversible. As a result it is frequently employed in doses that do not depress the marrow function, but at such low levels, it produces little or no anti-tumor effect.

6) Myleran: This sulfonic acid ester is the most effective oral agent now available for the treatment of chronic myeloid leukemia. Either as intermittent therapy or maintenance therapy, it offers control of the disease comparable to that obtained with irradiation therapy. Myleran also has proved effective in the treatment of polycythemia vera.

7) Amethopterin: (Methotrexate®): This folic acid antagonist was effectively employed in the treatment of acute leukemia in children. It has a specific role in metastatic trophoblastic tumors (choriocarcinoma) in women. Complete remissions of more than three years have been reported. Methotrexate is ineffective in choriocarcinoma in men; in women this is a homologous tumor. Following damage by Methotrexate, the formation of antibodies against the tumor foreign body may result in total destruction of the tumor.

8) 6-Mercaptopurine: Of the purine analogs this agent remains an effective drug for the treatment of acute leukemia. Though it is a depressant of bone marrow function, when carefully administered for short periods of time, it has produced significant remissions.

9) 6-Fluorouracil (see below)

10) Hormonal therapies: The control of prostatic cancer and of advanced cancer of the male and female breast by ablative hormonal therapies or administered hormones has been well established. No attempt will be made here to review these methods. Many hormonal agents have been introduced because they presumably have fewer undesirable side effects, provide as good or better anti-tumor effect, and offer greater ease of administration. Despite the number of new agents, those that remain most useful are: a) androgens: testosterone propionate (i.m.) or fluoxymesterone (oral), b) estrogens: stilbestrol (oral), and c) adrenal steroids: cortisone or prednisone.

11) Urethane: Ethyl carbamate is one of the oldest of the chemotherapeutic agents and is employed primarily in the
treatment of multiple myeloma. Good results are obtained when
the white blood cell count is maintained around 2500 per cu.
mm.

12) Radioactive isotopes: Though not true chemotherapeuti-
cic agents, the isotopes have specific use. Phosphorus\textsuperscript{32} is effec-
tively employed in the treatment of polycythemia vera; radio-
active Gold is used intraperitoneally following the removal of
large ovarian tumors with probable seeding of implants on the
peritoneum; and Iodine\textsuperscript{131} is employed in a rare patient with
thyroid carcinoma, if the tumor takes up a significant amount
of the tagged iodine.

**Current Investigations**

Clinical investigations of newer chemotherapeutic agents
have been carried out. Concomitantly with pilot studies of un-
proved agents, evaluation of potentially useful agents intro-
duced by other investigators is necessary, as is the assessment
of the clinical role of these agents. These studies can be made
independently or in cooperation with the National Cancer
Chemotherapy Service Center of the United States Public
Health Service. Evaluation of four such agents have recently
been made, in the literature and at the University of Minnesota
Hospitals.

A. Cyclophosphamide; (Cytoxan\textsuperscript{®}, Endoxan):

Cyclophosphamide is an alkylating agent synthesized in
1957.\textsuperscript{2} The biologic activity is attributed to the bis (2-chlo-
oroethyl) group. Preliminary studies in humans suggested that
this compound had a spectrum of anti-tumor activity similar to
that of nitrogen mustard but that it was less toxic. Extended
studies employed a wide variety of dose schedules ranging
from 100 mg. daily doses given orally to 8,000 mg. "loading"
doses given intravenously. This variability led to conflicting
reports as to the degree of toxicity and the anti-tumor effect.
Most patients tolerated 100 to 150 mg. per day either orally
or intravenously without incident. Above 200 mg. daily,
gastrointestinal effects were noted. Some observers regarded
cyclophosphamide more effective when given intravenously
than when given by mouth.\textsuperscript{3}

Anorexia, nausea, and vomiting occur with increasing fre-
quency as the dose is increased. A leukopenia below 3,000/cu.
mm. was frequently observed, but a rise to normal white count
was seen generally within a week after therapy was discon-
tinued. The recommendation has been to maintain the white
blood count between 2,000 and 4,000 cells per eu. mm. Partial
and transient alopecia occurred in up to 50 per cent of patients. One of the striking features has been the absence of thrombocytopenia. Decrease of platelets was reported only when 100 mg/Kg was given intravenously.

A review of European literature on the effect of cyclophosphamide in 51 patients with various hematologic tumors indicated that 38 (74 per cent) had tumor regressions. Of these, 14 patients (27 per cent) were adjudged to have responded favorably. Other investigators have reported excellent anti-tumor effects in 18 (38 per cent) of 95 patients, and in 8 (32 per cent) of 25 patients. Most of the tumors which responded were lymphomas and leukemias, but occasionally solid tumors also improved. The anti-tumor activity of cyclophosphamide was thus demonstrated.

A study of one dosage system in cyclophosphamide therapy was undertaken at the University of Minnesota Hospitals. After preliminary testing, an intravenous dose of 15 mg/Kg/week was chosen as the most workable. Attempts to give 30 mg/Kg/week resulted in a leukopenia below 500 cells/cu. mm. level. The schedule provided for weekly doses as long as the white blood count was higher than 2,000 per cubic millimeter. Most of the 49 patients chosen to receive this agent had been refractory to treatment with other cytotoxic agents or irradiation.

The results of this study were as follows: In 19 patients with solid tumors, no objective regressions occurred. One patient with an astrocytoma of the brain displayed remarkable sub-

**TABLE 1**

<table>
<thead>
<tr>
<th>Effect of Cyclophosphamide in Hematologic Tumors</th>
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<tbody>
<tr>
<td><strong>Tumor</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
</tr>
<tr>
<td>Reticulum Cell Sarcoma</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
</tr>
<tr>
<td>Erythroleukemia</td>
</tr>
<tr>
<td>Lymphatic Leukemia (Subacute)</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
jective improvement. Objective regressions occurred in 12 (40 per cent) of 30 patients with various hematologic tumors—all in the lymphoma group (Table 1). Among the entire 49 patients, the objective regression rate was 24 per cent. Of the 12 regressions observed, six were moderate and six striking. The period of control of the latter has been from six to 26 weeks at this date. Though objective improvement did not occur in the three patients with multiple myeloma, definite subjective improvement was noted in these patients.

Among side effects, nausea and vomiting occurred in 28 patients (57 per cent) following the injection, and anorexia lasted one to three days. Alopecia was noted in four patients (8 per cent), and fever in three. Leukopenia, with white cell counts varying from 100 to 4,500 per cu. mm. occurred in at least 40 patients with sufficient white blood counts to be adequately evaluated. Of 30 patients with multiple platelet counts, a decrease of more than 50,000 platelets per cu. mm. occurred in 10 patients. Only two of these patients, however, gave values below 100,000. Three patients with initial platelet counts below 30,000 had no further decrease nor bleeding tendency. In three patients the platelet count increased by more than 50,000/cu. mm.

In conclusion, cyclophosphamide is seen to be an alkylating agent whose anti-tumor activity is primarily effective in the lymphoma group. Among the 49 advanced cancer patients treated, all of whom had proved refractory to other chemotherapy agents, 12 experienced remissions. This agent, unfortunately, does produce alopecia as well as gastrointestinal reactions. Because of its characteristic failure to induce thrombocytopenia, it has special value in patients with lymphoma or chronic lymphatic leukemia in whom thrombocytopenia already exists.

B. 5-Fluorouracil:

The utilization of pyrimidines in the synthesis of nucleic acid has resulted in investigations of their chemical analogs in the chemotherapy of advanced malignant lesions. The most potent fluorinated pyrimidine is 5-fluorouracil (5-FU). The rationale for the investigation of 5-FU was based on the observation by Rutman et al. that uracil was utilized preferentially for nucleic acid biosynthesis in some tumors. When uracil is methylated at the "5" position, thymine is formed. Other investigators then demonstrated that 5-fluorouracil inhibited conversion of C¹⁴ labeled formate into the methyl group of thymine and also inhibited thymidilate synthetase. In effect,
5-FU created a thymine deficiency, thereby inhibiting the synthesis of deoxyribonucleic acid (DNA). Favorable preliminary reports led us to conduct a clinical evaluation.

In our clinical investigation, 5-fluorouracil was administered to 118 patients with the following advanced malignant disease: breast 43, colon 12, ovary 8, stomach 7, kidney 7, lymphoma 7, melanoma 4, neuroblastoma 4, lung 2, bladder 2, leukemia 2, sarcomas 6, metastatic carcinomas of unknown primary tumor 5, and one carcinoma each of the uterus, cervix, parotid, testis, adrenal cortex, nasopharynx, gallbladder, pancreas, and a carcinoid tumor.

Five daily injections of 5-FU, 15 mg/Kg of ideal body weight were given intravenously; one dose of 7.5 mg./Kg was given every two days thereafter until evidence of toxicity appeared. As the investigations proceeded the dose was limited to a maximum of five injections and a maximum daily dose of one gram. Subsequent courses consisting of one or two fewer injections than given in the initial dose were administered at periods of four to six weeks.

Results: Stomatitis (in 75 per cent of patients) was one of the earliest signs of toxicity. It began as dryness of the mouth and lips with hyperemia of the mucosa, and progressed to ulcerations of the lips and mouth. The kind of alteration observed in the oral mucous membrane was characteristic of the entire gastrointestinal tract. Diarrhea (in 65 per cent of patients) during the second week of therapy consisted of soft bowel movements or watery stools, and (in two patients) adynamic ileus; in two other patients the profound diarrhea resulted in shock and death. The intestinal mucosa was destroyed throughout the bowel in these two latter patients. Occasional dermatological changes occurred, consisting of erythema, scaling or bullous formation. Nail changes developed. Alopecia of varying degree (in 57 per cent) occurred after the acute phase, but hair regrowth occurred even when repeated courses of 5-FU were given. Hematopoietic depression was reflected in the peripheral blood in the form of leukopenia (87 per cent) of less than 4,000, mild thrombocytopenia (83 per cent) and mild anemia. The average time of maximum leukopenia was 16 days after the first dose of 5-FU (Figure 1). Levels as low as 100 WBC/cu. mm. were recorded. Adrenal steroids had no effect in stimulating the leukocytes. Prophylactic antibiotic therapy was employed if ulcerated skin lesions were present, and modified protective isolation was begun when the white blood cell count was below 1,000 per cu. mm. The thrombocytopenia
was mild, only two patients dropping below 50,000/cu. mm. Fever occurred during the end of the second week, but the presence of bacterial infection could rarely be established. The fever appeared to be a general toxic phenomenon and did not respond to antibiotic therapy. Seven deaths (6 per cent mortality rate) occurred as a result of therapy.

Among the 118 patients to whom 5-FU was administered, 87 showed no objective improvement. Definite shrinkage of tumor occurred in 31 patients (26 per cent). Regressions lasting less than two months occurred in 13 patients, the regressions being correlated with the severe toxic reactions. Regressions lasting two to six months occurred in six patients. Twelve patients (10 per cent) had improvements lasting more than six months, five of which were greater than one year. Of the 118 patients, 107 have died. Those patients demonstrating improvement survived longer than those who did not respond to this agent. The largest homogeneous group of tumors in this series was breast cancer. Of 43 patients with breast cancer 18 improved after treatment; nine of these had improvements lasting more than
six months, and among these, four had improvements lasting beyond one year.

It is apparent that 5-FU is able to produce shrinkage of tumor in a variety of malignant tumors. This response follows administration of a maximum tolerated or sublethal dose of 5-FU and is usually associated with severe toxicity. Shrinkage of tumor was noted in tumors of the ovary, colon, stomach; in neuroblastoma, undifferentiated carcinomas, Ewing’s sarcoma, and lymphoma. Significant objective regressions occurred in cancers of the breast, ovary, and one undifferentiated carcinoma of unknown primary origin. A similar regression rate of 10 per cent for improvements maintained more than six months has been recorded for 1233 patients with carcinoma of the breast, colon, and rectum (carcinomas assembled from a large group of investigators pooled data\(^1\)). It would appear that 5-fluorouracil has a limited role in the treatment of selected patients with advanced breast cancer not responsive to hormone therapy, and patients with ovarian carcinoma and hepatomas. The effectiveness in carcinoma of the colon is not impressive.

C. Uracil Mustard; 5-bis-(2-chloroethyl)-aminouracil.

Uracil mustard is an analog of nitrogen mustard in which the methyl group has been replaced with a physiologically active group, uracil. Following a demonstration of its anti-tumor effect in animal tumors, it was made available to us for clinical trial.

Fifty patients with hematologic tumors have been treated. Initially small doses were employed in 14 patients. In 30 patients the dose was 10 mg. a day (divided into two doses) for three days. The therapy was repeated at monthly intervals until maximum regression was obtained.

Objective improvement occurred in 31 (62 per cent) of the 50 patients treated (Table 2). The types of improvement were

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients Treated</th>
<th>Objective Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Lymphoblastoma</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

*Kindly supplied as U-8344 by Dr. James Lawson, the Upjohn Company, Kalamazoo, Michigan*
qualitatively similar to those seen with nitrogen mustard. In seven patients the disease has been controlled for more than a year. Those patients demonstrating objective improvements after uracil mustard therapy have survived at least two to three times as long as those failing to respond.

The systemic effects of oral uracil mustard were relatively mild. Gastrointestinal symptoms (in 42 per cent of patients), including anorexia, nausea, or vomiting occurred on the days of therapy and were less intense than those noted with nitrogen mustard. Leukopenia (in 38 per cent of patients) was maximally observed between the seventh and sixteenth days after therapy; the white blood cell count fell below 1,000/cu. mm. in only one patient. Thrombocytopenia (in 43 per cent of patients) of greater than 50 per cent of the initial level did not result in excessive bleeding. The return of the platelet count to fully normal levels appeared prolonged.

Uracil mustard has proved to be a useful oral alkylating agent with therapeutic effectiveness similar to that of other mustard analogs. The administration of large doses for short courses at intermittent periods provides simple therapy for chronic lymphatic leukemia and malignant lymphoma.

D. Progestational Agents: 17-alpha-hydroxyprogesterone caproate

The profound effect of progesterone on the normal endometrium, and the demonstration of regressions of certain cancers upon alteration of hormonal balance in patients, have led investigators to employ progestational agents in the treatment of endometrial carcinoma. Six of 21 patients treated with prolonged courses of progestational agents showed objectively evident regressions lasting from nine months to four and one-half years.12

A synthetic progestational agent, 17-alpha-hydroxyprogesterone caproate, has been administered to 14 patients with advanced endometrial carcinoma at the University Hospitals. Intramuscular doses of 250 mg. to 500 mg. three times a week have been employed. No systemic reactions were observed, but tender nodules in the buttocks occurred in one patient.

Results: Three of 14 treated patients have had striking objective regressions with disappearance of pulmonary metastases or decrease in the amount of pelvic disease for periods of 4.5+, 11+, and 15+ months. Two patients have been treated for a period too short to evaluate the response. Eight patients have

*Kindly supplied as Delalutin® by Dr. E. C. Reifenstein, E. R. Squibb and Sons, New York City.
died within four and one-half months of the onset of therapy. One patient with pelvic disease only has not responded after five months of therapy.

The mechanism of action of this progestational agent in inducing tumor regression is unknown. Disease recurring in areas of prior intense irradiation may not respond as effectively as metastases occurring in nonirradiated regions. The anti-tumor effect of 17-alpha-hydroxyprogesterone caproate in endometrial carcinoma provides a new therapy for this disease.

DISCUSSION

The continual introduction of new chemotherapeutic agents for the control of advanced malignant lesions necessitates comparative evaluation of agents already in vogue and of the newer compounds (Table 3). It is increasingly obvious that many agents may have antineoplastic activity for specific tumors. Hence, in patients with disseminated disease an attempt to determine the site of the primary lesions is mandatory. The type of tumor, site of metastases, and general status of the patient will determine the selection of the specific therapeutic agent.

Administration of chemotherapeutic compounds may result in retardation of the rate of tumor growth or fleeting shrinkage of tumor masses. Significant objective regressions are those maintained for at least two months beyond the period of recovery from general toxic reactions. Repeated doses at regular intervals may maintain tumor control.

Since up to this point quantitative differences have been demonstrated between normal and cancer cells, it is doubtful whether any single agent will have sufficient specificity of action to control the disease indefinitely. Sequential blocking of different levels of several metabolic pathways essential for tumor cell growth appears to be a rational procedure.

Combinations of therapy have already been attempted. Two or three chemical agents have been administered simultaneously, or a chemical agent has been used in combination with irradiation therapy. Though favorable responses occur, the task of evaluating the true effectiveness of this therapeutic approach is monumental. Such therapies require a large series of patients and careful management of the many variables.

Recent clinical investigations have focused on four new chemotherapeutic agents. Cyclophosphamide is an effective alkylating agent for the treatment of lymphomas. It appears to be less toxic than nitrogen mustard and is easier to regulate. Its failure to induce thrombocytopenia provides a specific advant-
| Substance               | Hodgkin's Lymphoma | Lymphoblastoma | Neuroblastoma | Mycosis Fungoides | Chronic Leukemia | Acute Leukemia | Multiple Myeloma | Prostate Cancer | Breast Cancer | Colon Cancer | Endometriosis | Choriocarcinoma | Ovary Cancer | Lung Cancer | Thyroid Cancer |
|-------------------------|--------------------|----------------|---------------|-------------------|------------------|----------------|-----------------|----------------|--------------|--------------|----------------|----------------|-------------|--------------|
| Nitrogen Mustard        | ++                 | ++             | ++            | ++                | ++               | ++             | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Uracil Mustard          | ++                 | ++             | ++            | ++                | ++               | ++             | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Chlorambucil            | +                  | +              | +             | +                 | +                | +              | +               | ++             | +            | ++           | +              | ++           | ++          | ++           |
| Cyclophosphamide        | ++                 | ++             | +             | +                 | +                | +              | +               | ++             | +            | ++           | +              | ++           | ++          | ++           |
| Thio-TEPA               | +                  | +              | +             | +                 | +                | +              | +               | ++             | +            | ++           | +              | ++           | ++          | ++           |
| Busulfan                | ++                 |                |               |                   |                  |                | +               | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Amethopterin            |                    | +              | +             |                   |                  |                | +               | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| 6-mercaptopurine         |                    |                |               |                   |                  |                | ++              | ++             | +            | ++           | ++             | ++           | ++          | ++           |
| 5-fluouracil            |                    |                |               |                   |                  |                | +               | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Androgens               | ++                 |                |               |                   |                  |                | +               | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Estrogens               | ++                 |                |               |                   |                  |                | +               | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Corticoids              | ++                 | ++             | ++            | ++                | ++               | ++             | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Progestines             | ++                 | ++             | ++            | ++                | ++               | ++             | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Urethane                |                    | ++             | ++            | ++                | ++               | ++             | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| p32                     |                    | +              | +             |                   |                  |                | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| j321                    |                    | +              | +             |                   |                  |                | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
| Au¹⁹⁸                  |                    |                |               |                   |                  |                | ++              | ++             | ++           | ++           | ++             | ++           | ++          | ++           |
AGE when treating patients with depressed marrow function. **Uracil mustard** is an oral alkylating agent for the treatment of lymphomas and chronic lymphatic leukemia. The administration of large doses for a short period of time provides a simple therapy for these diseases. A third agent, **5-Fluorouracil**, is a relatively toxic anti-metabolite with limited use in selected patients with ovarian carcinoma, with hepatoma, or with advanced breast cancer which is refractory to hormone therapy. Finally, **17-alpha-hydroxyprogesterone caproate** is an effective hormone in the treatment of advanced endometrial carcinoma.

**Acknowledgement:** The investigators wish to acknowledge the aid of Dr. Velta Mikelsons for the hematologic studies, Miss Ann Black for biochemical studies, and all the staff members of the Masonic Memorial Hospital for their remarkable efforts in patient care.

**REFERENCES**


INTRODUCTION

Great progress has been made in clarifying the histologic classification of the various tumors or tumorous conditions of bone in the past twenty years.\textsuperscript{1–3} Our objective is confined to a review of the primary tumors of bone seen at the University of Minnesota Hospitals during the 17 year period from 1940 through 1956. Correlation of tumor incidence and five year survival to accepted standards is made where particularly meaningful. The definition of primary bone tumor as used in this text is, "a neoplastic or tumorous condition arising from the skeletal system primarily, though not necessarily only, from osseous tissue."

METHODS AND MATERIALS

A search through the pathologic, roentgenographic, and medical record files furnished the basis of the study. Only cases with histologically proved diagnoses were used. Individual patient charts were reviewed and the pertinent clinical data extracted. A follow-up of the malignant tumors was obtained in all cases, usually to within recent months. No cases of multiple myeloma or leukemia are included. The only cases included from the lymphosarcoma group are those in which the primary bone origin appeared obvious after intensive investigation. Tissue slides from all patients who had survived malignant tumors were carefully reviewed by the Path-
ology Department for accuracy of diagnosis. (Survival as used in this paper refers to the accepted five year standard.)

RESULTS

This study produced 155 usable cases. These included 67 (43 per cent) benign and 88 (57 per cent) malignant lesions as defined by current standards.

TABLE 1
ANALYSIS OF ALL CASES OF BONE TUMOR BY INCIDENCE AND AGE GROUP

<table>
<thead>
<tr>
<th>Age-Decade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total &amp; Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>5</td>
<td>24</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>63-43</td>
</tr>
<tr>
<td>Malignant</td>
<td>8</td>
<td>29</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>14</td>
<td>3</td>
<td>88-57</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>53</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>15</td>
<td>19</td>
<td>5</td>
<td>155-100</td>
</tr>
</tbody>
</table>

TABLE 2
ANALYSIS OF BENIGN BONE TUMORS BY INCIDENCE AND AGE

<table>
<thead>
<tr>
<th>Age-Decade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total &amp; Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteochondroma</td>
<td>2</td>
<td>19</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>40-60</td>
</tr>
<tr>
<td>Giant Cell Tumor</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic Granuloma</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5-7</td>
<td></td>
</tr>
<tr>
<td>Chondroma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoid Osteoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odontoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adamantinoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonossifying Fibroma</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoma</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant Osteoid Osteoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>24</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>67-100</td>
</tr>
</tbody>
</table>

313
Osteochondromas (simple exostosis, osteocartilaginous exostosis)

As in other series, this was the most commonly encountered form of benign tumor, accounting for 40 cases (60 per cent) of benign lesions. The ratio of male to female patients was 23/17. The average age was 26 years, and the complaint of a bony mass was typically present for six years. Eighteen cases of tumor were found on either side of the knee, six in the proximal humerus, and four in the pelvis. The remainder were in varied locations but usually located at the end of a long bone. Simple excision nearly always produced a permanent cure. There were two cases of recurrence.

Giant Cell Tumor (Osteoclastoma)

This controversial lesion was identified in seven cases (10 per cent) of benign lesions, with a male to female ratio of 3/4. The average patient age was 40 years. Pain was the prominent symptom with an average duration of five months. Five of the seven patients were followed for an average of six years without recurrence, the remaining two being lost to follow-up study. Therapy consisted of amputation in two cases, excision and curettage in four, and irradiation of 2000 r/tumor in one case. The usual location was at the end of a long bone.

Eosinophilic Granuloma

The most innocuous of the three commonly described patterns of reticuloendotheliosis in histiocytosis X, is usually a solitary and curable granuloma. Schüller-Christian syndrome and Letterer-Siwe's disease are the usually fatal components of the triad. Eosinophilic granuloma is considered to be limited to an osseous lesion. It was identified in five cases (7 per cent) with a male to female patient ratio of 5/0. The usual symptom of pain or mass or both was present for an average of seven months. The average age of these patients was 26 years. Treatment consisted of excision, irradiation, or both. The follow-up in four cases averaged 5.5 years without recurrence; the fifth patient was lost to follow-up study.

Chondroma

Only three cases of this benign lesion composed of mature hyaline cartilage were found. The average age of these patients was 44 years. One lesion was excised in the mandible, and two were excised in the ribs. One patient, whose rib lesion measured 40 x 25 x 20 cm., had no recurrence after twelve years. No follow-up could be obtained on the other two patients.
Osteoid Osteoma

This lesion is described as a small osteoblastic nidus often surrounded by sclerotic bone. The three patients having this lesion complained of pain for an average of 12 months. Their average age was 18 years. Therapy in all cases consisted of excision, with no observed recurrence during an average follow-up period of three years.

Adamantinoma (Ameloblastoma)

All three cases of this peculiar epithelial tumor of the mandible were treated by excision of the primary tumor. Recurrence was seen twice in one case and once in another case. Re-excision of these recurrent lesions ultimately provided a cure. The average patient age was 60 years, and the symptom of a mass was present on the average for 12 years. No cases of this lesion were found in long bones. The follow-up period averaged eight years.

### TABLE 3

**Analysis of Malignant Tumors by Incidence and Age**

<table>
<thead>
<tr>
<th>Age-Decade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total &amp; Per cent</td>
<td>8</td>
<td>29</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>

- **Osteogenic Sarcoma**: 6 19 7 4 4 2 3 1 46-57
- **Ewing's Sarcoma**: 1 8 2 1 12-14
- **Chondrosarcoma**: 1 2 2 3 8-9
- **Fibrosarcoma**: 1 2 4 7-8
- **Undifferentiated Sarcoma**: 1 2 3
- **Reticulum Cell Sarcoma**: 1 2 3
- **Lymphosarcoma**: 1 2 3
- **Chordoma**: 1 1 2
- **Malignant Synovioma**: 1 1 2
- **Hemangiosarcoma**: 1
- **Hemangiendothelioma**: 1

**Total**: 8 29 11 8 8 8 13 3 88-100

315
Miscellaneous

Included in the series of benign tumors are two odontomas of jaws, two osteomas of the clavarium, one nonossifying fibroma occurring in a rib, and one giant osteoid osteoma of the third thoracic vertebrae, originally misdiagnosed at open biopsy as an osteogenic sarcoma. Review of the original slides following a 17 year survival prompted reclassification into the category of a benign lesion.

Osteogenic Sarcoma

To fulfill this diagnosis, in its structure a malignant tumor of bone must show osteoid tissue which is produced by the sarcomatous cells of the neoplasm. Forty-six such cases were found, with a male to female ratio of 33/13, and an average patient age of 24 years. The symptoms of mass and pain were present for an average of four months. Twenty-six of the cases occurred in the age group of 10-30 years. The area about the knee accounted for 23 (50 per cent) of the tumors. The proximal femur, the proximal humerus, and the pelvis each accounted for four tumors. The remaining tumors were seen in nearly all bones, though most commonly at the end of a long bone.

**TABLE 4**
**Summary of Methods of Therapy**

<table>
<thead>
<tr>
<th>Method</th>
<th>Total</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Surgical Therapy</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>2. Irradiation</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>3. Surgical Therapy and Irradiation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4. Treatment Refused</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>46</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

**TABLE 5**
**Relation of Survival to Interval Between Biopsy and Surgical Intervention**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Total</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Biopsy and surgery</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. 1-2 day interval</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3. 3-7 day interval</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>4. More than 7 days</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

316
Seventeen patients died during the first year after therapy, ten patients during the second year, and six during the third; three patients lived to four years. There were ten survivors, with an average follow-up period of 12.3 years. The survival rate has been 21.7 per cent. A large series of 353 patients with a five year follow-up was reported by Coventry and Dahlin of the Mayo Clinic as having a 19.3 per cent survival rate.

Ewing's Sarcoma

The twelve patients (four male, eight female) had an average duration of pain or mass or both for four months before diagnosis and an average age of 16 years. The tumor was observed to arise from a long leg bone in nine instances. The therapy consisted of amputation above the knee in one case, irradiation in eight cases, and a combination of excision and irradiation in one case; therapy was refused in one case. Of the two surviving patients, both had been treated solely by radiation (4,500 r/tumor in one case and 4,850 r/tumor in the other). The survival rate has been 16.6 per cent. Eight patients died within two years. One individual with tumor in the distal fibula was not counted as a five-year survivor; he lived for fourteen years after above-knee amputation. During this time, he underwent eight thoracotomies for the removal of more than thirteen metastatic tumor nodules within the lungs.

Chondrosarcoma

The eight cases were all treated surgically—four by amputation and four by radical excision necessitated by the location of tumor in the ribs or vertebral column. Three of the patients lived more than five years after therapy, although one has recently undergone surgical treatment for a recurrent tumor seven years after hemipelvectomy. The criterion of five year survival is of little value when applied to this tumor because of the slowness of tumor growth. One patient had five large masses resected from the chest wall during the eighteen years before his death. The average patient age was 48 years, with symptoms of mass and pain present for an average of 1.3 years. One of the patients had Ollier’s disease with secondary chondrosarcoma arising in the talus.

Fibrosarcoma

Only one of the seven patients survived. These patients averaged 57 years of age, with the usual symptoms of pain
present for five months. Amputation was performed in all seven cases.

**Undifferentiated Sarcoma**

Three cases were encountered. The average patient age was 56 years with symptoms present for only two months before diagnosis. Two of the three patients were treated by irradiation, the other by surgical therapy. All three died within two years. These tumors were found in the proximal humerus, the ilium, and the seventh rib.

**Reticulum Cell Sarcoma**

This lesion is often difficult to distinguish from Ewing's sarcoma. The three patients averaged 58 years of age and had had symptoms for an average of nearly a year before diagnosis. Excision was performed in one case in which the neoplasm was in the fibula; the other two tumors (one in the occiput and one in the sacrum) were treated by irradiation. The sole 15 year survivor had been given 4,500 r/tumor to the sacrum.

**Lymphosarcoma**

All three patients died within two years. The average age at diagnosis was 42, and the symptoms of pain, mass, or both were present for an average of three months. Either excision or irradiation was employed. The tumors were seen in the sternum, the pelvis, and the second lumbar vertebra.

**Chordoma**

Two patients were seen with this tumor in the sacrum. One was alive 15 years later with one recurrent tumor having been excised five years after the original radical excision. The other patient died five years after radical excision, from a large locally recurrent tumor. The patients averaged 52 years of age, and each had noted a painful mass for slightly more than one year.

**Synovioma**

There is no distinction histologically between malignant synovioma and synovioma. Both of the patients exhibiting this malignant neoplasm died within five years. Therapy consisted of amputation in one patient and amputation combined with irradiation in the other. The average patient age was 62 years.

**Miscellaneous**

Of the two remaining patients with malignant tumors, one was a child with an iliac hemangiosarcoma which was treated
by irradiation; the child died within a year. The other patient was a young man with hemangioendothelioma; he has survived for 21 years after shoulder disarticulation followed in two years by scapular resection for recurrence.

Summary

A 17 year study of the primary bone tumors treated at the University of Minnesota Hospitals is presented. Multiple myeloma and the leukemias are excluded, and only those cases having histologic proof of diagnosis are included. The resulting series is composed of 155 tumors consisting of 67 (43 per cent) benign and 88 (57 per cent) malignant neoplasms.

Pertinent clinical data, method of treatment, and length of follow-up are described for each specific tumor group where possible. One hundred per cent follow-up has been obtained for the malignant lesions, and all five year survivors of malignant disease have had their tissue slides reviewed to insure accuracy of diagnosis.

The overall five year survival among the malignant tumors is 20.4 per cent (18/89). Survival for osteogenic sarcoma is 21.7 per cent (10/46), and survival for Ewing's sarcoma is 16.6 per cent (2/12).

References

PAUL G. QUIE NAMED MARKLE SCHOLAR

Dr. Paul G. Quie, assistant professor of pediatrics, has been named the recipient of a $30,000 John and Mary R. Markle Foundation award.

He is the twelfth Minnesotan to receive the highly-prized Markle Scholar honor, given annually to outstanding young men of medical science. The program is designed to help relieve the faculty shortage in medical schools by giving younger teachers and investigators academic security and financial assistance early in their careers. Under the award, the University of Minnesota Medical School will receive $6,000 a year for the next five years, toward support of Dr. Quie and his research.

Twenty four other Markle Scholars were appointed this year at U. S. and Canadian medical schools under a fund established in 1927 by the late John Markle, a Pennsylvania coal operator.

Dr. Quie's Markle appointment is effective July 1, 1961. He is a native of Dennison, Minn., and received his premedical education at St. Olaf college. He graduated from the medical school of Yale University in 1953, and was an intern at Minneapolis General Hospital before spending 1955-57 as a medical officer in the U. S. Navy. He was appointed an instructor in the Medical School's department of pediatrics in 1958.

In his research, Dr. Quie has made substantial contributions in the areas of the fibronolytic (plasmin-plasminogen) system of the newborn, and on the staphylococcal Muller factor. He is 36 years old, married, has three children, and lives in St. Paul, Minn.

Previous winners of Markle Scholar honors while at Minnesota were: Drs. Leonard Peltier, Gilbert Campbell, Lloyd MacLean, Mitchell Spellman, Richard Egdahl, George E. Moore, Russell Nelson, William Scherer, Robert Ulstrom, Robert A. Good, and Richard C. Lillehei.
DR. RUTH BOYNTON RETIRES

Dr. Ruth E. Boynton has retired effective June 30, 1961, as Director of the Students Health Service at the University of Minnesota, completing a 25-year medical career devoted for the most part to keeping college students healthy.

"I'm retiring voluntarily after 25 years," Dr. Boynton said, "so that I have time to travel while I'm still hale and hearty." She received her medical degree from the University of Minnesota in 1921. With the exception of a single year spent at the University of Chicago Students Health Service, she has been at the University of Minnesota ever since.

Dr. Donald W. Cowan, Assistant Director since 1936, has been named as Professor and Director of the Students Health Service, succeeding Dr. Boynton, effective July 1, 1961. Dr. Benjamin R. Reiter, Associate Professor of Public Health and Health Service surgeon, will become assistant director to succeed Dr. Cowan.

Dr. Boynton joined the University staff as an assistant to the director of the health service in 1921, and became director of the unit in 1936. She is the author of more than 85 papers on subjects relating to the health of college students, and holds the rank of Professor of Public Health at her retirement.

Dr. Boynton received the 1961 Francis E. Harrington Award of the Minneapolis Junior Chamber of Commerce for outstanding service in the field of public health.

The new director, Dr. Cowan, joined the University staff in 1928. An allergist, he has conducted extensive research and written several papers on "the common cold," including use of vaccines and use of vitamins in treatment and prevention. He received his medical degree from the University in 1931.

Dr. Reiter is a 1934 graduate of Harvard Medical School, and joined the University staff as a physician and instructor in School of Public Health in 1956.

Both men hold the rank of associate professor.
PEDIATRICS

Dr. Robert A. Good, Professor, delivered the annual Walter B. Seelye Lecture at the University of Washington Medical School on March 21, 1961. His topic was “Progress in Homotransplantation.”

BACTERIOLOGY

Dr. Herman C. Lichstein, Professor, gave a Sigma Xi lecture on March 24, 1961 at the University of Tennessee. As Visiting Scholar at the University of Georgia, Emory University, and Oglethorpe University March 27-30, he lectured on “Physiological Control Mechanisms in the Microbial Cell” and “The Biotin-Fatty Acid Relationship.”

ANATOMY

Dr. Arnold Lazarow, Professor and Head of the Department, addressed the Rochester, N.Y. Academy of Medicine on March 7, 1961. His subject was “Present State of our Knowledge Concerning the Etiology of the Complications of Diabetes.”

NEUROLOGY

Dr. Mavnard M. Cohen, Professor, has returned to the Medical School following a leave of absence. During a one-quarter leave, he lectured on chemistry of the brain at the Universities of Oslo and Copenhagen, and conducted research at the Istituto Superiore di Sanita, in Rome, Italy.

Dr. Cohen has received a grant of $140,448 from the U.S. Public Health Service to conduct a three-year research program in neurochemistry beginning July 1, 1961. He also received a U.S.P.H.S. grant for research on cerebral morphology and metabolism in vitro.

Dr. Birger Kaada of the Anatomical Institute, University of Oslo, Norway, is serving as Visiting Professor at the University of Minnesota Medical School through December 31, 1961. He is engaged in graduate teaching and investigation in electroencephalography and neurophysiology in the Division of Neurology.
LABORATORY OF PHYSIOLOGICAL HYGIENE

Dr. Ancel Keys, Director, delivered lectures on Diet and Coronary Heart Disease at the University of Syracuse Medical School March 28 and at the Annual Medical Assembly of the Southeastern Massachusetts Heart Association at New Bedford March 29. On April 7 he addressed the annual meeting of the American Epidemiological Society at Atlanta, Ga., and on April 23 the Third Yugoslav Congress on Cardiology at Opatija, Yugoslavia, the title in both cases being the Risk of Coronary Heart Disease. At Opatija, Dr. Keys also chaired a series of conferences with collaborators in research, coordinated from the University of Minnesota, from Finland, Sweden, Denmark, Holland, Yugoslavia, Italy and Greece.

CANCER BIOLOGY

Dr. John J. Bittner, Professor of Cancer Research and Experimental Pathology, has been invited to contribute a paper on “Mammary Cancer in Mice” for a program on cancer by Radio-diffusion-Television Française for the International University of the Air. The I.U.A. is maintained jointly by a number of western European broadcasting systems for the exchange of information on subjects chosen by its General Assembly. Dr. Bittner’s manuscript will be translated into other languages and broadcast during the summer.

DERMATOLOGY

Dr. Robert W. Goltz, Clinical Associate Professor, presented two papers before the 13th Annual Midwest Cancer Conference in Wichita, Kansas, under sponsorship of the Kansas Division of the American Cancer Society.

MEDICINE

Dr. Wesley W. Spink, Professor, served as Professor of Medicine, pro tem, at the University of Alabama Medical College during the week of April 3. He also addressed the Birmingham Society of Internists.

SURGERY

Dr. Arnold J. Kremen, Clinical Professor, and Dr. W. Albert Sullivan, Jr., Assistant Professor, were elected to membership in the Central Surgical Association at its annual meeting February 16-18, 1961, in St. Louis, Mo.
Recent Faculty Publications


Donald Stanton Asp, Medical School freshman from Milaca, Minn., was named 1960-61 recipient of the Rural Medical Scholarship awarded annually by the Minnesota State Medical Association.

He will receive $1,000.00 each year for four years and in return promises to practice medicine for at least five years in a rural Minnesota area in need of a doctor. The dual purpose of the scholarship, according to MSMA, is to assist a worthy and outstanding student to meet the cost of a medical education, and to insure a future supply of physicians in non-metropolitan communities.

Asp was valedictorian of his high school class, and received his pre-medical college education at the University of Minnesota. He is the son of Mrs. John Asp of Milaca.

Four previous Rural Medical Scholarship recipients are now practicing medicine in rural areas of the state. They are: Dr. Richard Engwall, Tyler; Dr. Leland Christenson, Maple Plain; Dr. Myron Doebler, Bagley; and Dr. Carl E. Christenson, Clinton. Scholarship winners currently enrolled in the Medical School in addition to Asp are: George B. Gerstenkorn, Belgrade, sophomore; LeRoy Mueller, Belle Plaine, junior; and Edward S. Peterka, Aurora, senior. Dr. Vincent R. Hunt, 1956 recipient, is now interning at Bethesda Hospital, St. Paul.

FOREIGN FELLOWSHIP AWARDED

Gerhard J. Johnson, Medical School junior from St. Paul, was among thirty junior and senior medical students from across the nation named winners of foreign fellowships by the Smith Kline & French Laboratories. The program is administered by the American Association of Medical Colleges.

Johnson received a grant of $1,555.00 to spend October through December, 1961, working at Lutheran mission hospitals in Tanganyika. Under the supervision of his overseas sponsor, Dr. Joseph L. Norquist (Med. '53), he will study and combat diseases not commonly seen in this country. The Augustana Lutheran Mission serves a native population of over 300,000 in a remote rural area of Africa.
$70,000 ALUMNI FUND DRIVE UNDERWAY

The Minnesota Medical Alumni Association has launched a $70,000 fund drive among its members and other graduates of the Medical School to provide a Medical Student Center at the University.

The facilities will be established on the first level of the Mayo Memorial Building, site of the Medical School, for its 500-member undergraduate body. Dr. Virgil J. P. Lundquist (Med. '42), Minneapolis surgeon, was named general chairman of the project. Plans were announced and architectural sketches were shown May 4 at the annual Senior Class-Alumnus luncheon sponsored by M.M.A.A. Dr. Leonard W. Larson (Med. '22), Bismarck, N.D., pathologist and president-elect of the American Medical Association, was principal speaker.

The Medical Student Center will occupy some 3,500 square feet of remodeled space now used for storage on the first level of the Mayo Memorial building. It will provide:

- A "ready room" for advanced clinical medical students
begins Medical Student Center Project

assigned to the new Comprehensive Clinic program, where they will await calls, referrals, write case reports, etc.

• An area for medical student relaxation, rest, conversation, and refreshment. This facility will supplement, not replace, the facilities of the Coffman Memorial Union, and will be convenient to medical students in their own area of activity.

• Lunching and snack facilities for the majority of the medical student body who carry bag lunches. Lunch tables and some food vending equipment will be included.

• Additional racks and lockers for temporary storage of textbooks, valuable instruments, and other materials required in medical training.

Dr. Lundquist said students at the Medical School have actively assisted in the planning and development of the Medical Student Project, including architectural design. He said the Medical Alumni Association was concentrating its entire strength and resources on the project, and called on all graduates of the University of Minnesota Medical School for support. Complete details of the project and pledge cards are being sent to more than 5,000 medical alumni, he announced.
Project headquarters have been established in donated space in the Northwestern National Bank Building, Minneapolis 2, Minn. Contributions and pledges are now being received, Dr. Lundquist said. Miss Gertrude Olson of Minneapolis has been appointed volunteer campaign secretary, and Mr. Eivind Hoff, Jr., executive director of the Minnesota Medical Foundation, is serving as campaign consultant. The Greater University Fund and parent Minnesota Alumni Association are also cooperating.

Headquarters are open each weekday afternoon and the telephone number is FEderal 5-7191, Dr. Lundquist announced. He urged all medical alumni to support the campaign for funds, and described the effort as "the largest and most important project ever undertaken by the Medical Alumni Association." The campaign will continue until success is achieved, he said.

Members of the M.M.A.A. Board of Directors are serving as a core committee, and regional chairmen throughout Minnesota are now being appointed. Tentative plans call for opening the new facility in September, 1962.

DR. IRVIN KERLAN RECEIVES UNIVERSITY'S OUTSTANDING ACHIEVEMENT AWARD

Dr. Irvin Kerlan, native Minnesotan and 1934 graduate of the Medical School, received the University of Minnesota's Outstanding Achievement Award in special ceremonies in Minneapolis April 15, 1961. President O. Meredith Wilson bestowed the high honor in recognition of Dr. Kerlan's success in both his chosen field — medicine — and his avocation — collecting original illustrations, manuscripts, and first editions of children's literature, and encouraging publication and use of good books.

Dr. Kerlan received a medical degree from the University of Minnesota at the age of 21 years. He is now chief of the Research and Reference Branch of the U.S. Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C.

He is founder and sponsor of the Kerlan Collection of approximately 10,000 bound volumes of children's literature, most of which is permanently housed at the University of Minnesota. Dr. Kerlan has lectured widely and sponsored many literary exhibits based on the Kerlan Collection.
Alumni Notes

♦ 1905
Roy Lynde, retired general practitioner at Ellendale, N. D., is the subject of an article in the April 1961 Readers Digest. He is 86 years old and has spent his entire medical career in Ellendale.

♦ 1907
M. L. Strathern and Mrs. Strathern of Gilbert, Minn., celebrated their fiftieth wedding anniversary last fall and were honored by residents of the Gilbert area.

♦ 1921
Roger L. J. Kennedy has retired from the Mayo Clinic, Rochester after 26 years' service. He has been a specialist in diseases of children.

♦ 1926
Orvie J. Swenson was elected president of the Waseca (Minn.) County Medical Society. Dr. S. T. Normann (Med. '50) was named vice president and Dr. R. D. Davis (Med. '33) was chosen secretary-treasurer. All three physicians are from Waseca.

♦ 1928
Miland E. Knapp, chief of the department of physical medicine and rehabilitation at the Sister Kenny Rehabilitation Institute, was named president of the Institute's medical staff. Dr. Theodore Papermaster (Med. '38) was named secretary.

♦ 1930
Harvey T. Petraborg, who has practiced in Aitkin, Minn. for many years, was named recipient of the R. J. Bolen Outstanding Citizens Award by the Aitkin Lions Club.

E. G. Oppen has been appointed medical director of Security National Life Insurance company, Minneapolis. Dr. Oppen is engaged in the general practice of medicine.

♦ 1931
Russell C. Lindgren of Minneapolis was elected first vice president of the Hennepin County Medical Society, and Dr. J. H. Strickler (Med. '41), also of Minneapolis, was elected second vice president.

♦ 1932
George E. Cardle of Brainerd, Minn. was elected president of the Upper Mississippi Medical Society.
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• 1938
  Bernard J. Hughes has become associated in practice at St. Cloud, Minn. with Dr. Henry Broker, a general and thoracic surgeon. Dr. Hughes is formerly of Brainerd.

• 1939
  Col. Carl N. Ekman of the U. S. Army Medical Corps is retiring after 22 years of service to enter private practice in Tacoma, Washington. He has been Chief of the Gastroenterology Service and Assistant Chief of the Department of Medicine at Madigan General Hospital in Tacoma.

• 1940
  Wyman Jacobson of the St. Louis Park (Minn.) Medical Center has been re-elected president of the Twin Cities Diabetes Association.

• 1941
  Charles F. Brigham of St. Cloud was appointed Stearns county (Minn.) physician.

• 1941
  Julien V. Petit, Minneapolis internist, has been elected chief of the medical staff at Fairview Hospital. Dr. E. Robert Schwartz (Med. '36), and Dr. Harvey O’Phelan (Med. '44) were also elected staff officers.

• 1943
  Raymond A. Sanford has been re-elected president of the St. Joseph’s Hospital medical staff at Mankato, Minn. Dr. H. J. Setzer (Med. ’24) was named vice president, and Dr. O. D. Anderson (Med. ’55) was elected secretary.

• 1944
  Robert E. Nord is president of the medical staff at Methodist Hospital, Minneapolis.

• 1945
  George Martin was elected president of the Thief River Falls, Minn. Chamber of Commerce for 1961.

• 1946
  Rudolph B. Skogerboe, Karlstad, Minn. physician, was elected vice president of the Red River Valley Medical Society. Dr. Russell O. Sather (Med. ’33) of Crookston was reelected secretary-treasurer. Dr. Daniel Greene of Thief River Falls was named president.

• 1947
  John E. Verby of Rochester, Minn., was named vice president of the Olmsted Medical Group at its annual meeting. Ten physicians, including several other Minnesota graduates, are partners in the Olmsted Medical Group.
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1949
Alois M. Scheidel of Mankato, Minn. was named president of the Immanuel Hospital medical staff in that city. Dr. W. E. Mathews (Med. '58), also of Mankato, was elected secretary.

1951
George Rysgard, Northfield physician, was elected president of the Southern Minnesota Academy of General Practice for 1961.

Mark E. Odland has been elected chief of staff of the St. Mary's Hospital in Detroit Lakes, Minn. Dr. A. S. Midthune (Med. '46) was named vice president, and Dr. Robert Watson (Med. '44) was re-elected secretary-treasurer.

1952
Frank J. Carthey is new president of the Loretto Hospital medical staff at New Ulm, Minn.

1954
Wayne Campbell, Waseca physician, served as Waseca county chairman for the 1961 Heart Fund drive.

Vernon G. Kuhlmann was named president of Our Lady of Mercy Hospital at Alexandria, Minn. The hospital's medical staff includes 18 physicians.

1955
Capt. Donald C. Martin of the U. S. Air Force is a medical officer attached to the American Embassy in Moscow, U.S.S.R.

1957
George Bingham, Bird Island, Minn. physician and Renville county (Minn.) health officer, was elected chief of staff at the Renville County Hospital.

1958
Sheldon G. Cable was married recently to Betty Paula Herzfeld of Elizabeth, N. J. in San Francisco, Calif. Dr. Cable is the son of Dr. and Mrs. Morris L. Cable (Med. '26) of Minneapolis.

1959
Lt. Thomas R. Arlander has entered the U.S. Navy, Medical Corps, and been assigned to sea duty with Destroyer Division 222.

Lt. Rodger K. Nelson and Lt. John D. Riley of the U.S. Navy have completed their training at the Naval School of Aviation Medicine, Pensacola, Fla., and have gone on duty with the fleet.

Lt. Lawrence R. Ringhofer, Jr., U.S. Navy Medical Corps, assigned to the Navy Recruiting Station at Indianapolis, Indiana, has constructed a Polaris Missile Exhibit, which is in use by 17 Navy Recruiting Branch Stations in the Indianapolis area.
ALUMNI DEATHS

1910
Dr. Henry E. Binger died March 13, 1961, at the age of 75. He had practiced in St. Paul, Minn. for thirty years, specializing in otolaryngology.

1916
Dr. Oliver H. Peterson, former chief of staff at Swedish Hospital, (Minneapolis), died April 3, 1961. He had retired in 1959 following forty years in the practice of medicine. He was former medical director for the Association of Insurance Companies, and a director of the North American Life and Casualty Co. Dr. Peterson, 77 years old, was a charter member of Central Lutheran church of Minneapolis, and a member of Phi Beta Pi medical fraternity.

1925
Dr. Gerald M. Koepcke died March 30, 1961. He was 59 years old, and a member of the American and International College of Surgeons. Dr. Koepcke was a member of Our Saviour’s Lutheran Church of Excelsior, Minn.

1936
Dr. Halward M. Blegen, Jr. died April 2, 1961 at his home in Missoula, Mont. He was 48 years old and a native of Minneapolis. Dr. Blegen was the son of the late Dr. Halward M. Blegen, Sr. (Med. ’09), and a nephew of Theodore C. Blegen, dean emeritus of the University of Minnesota Graduate School.

Memorial Gifts

Memorial gifts to the Minnesota Medical Foundation have been received recently in memory of:

Mrs. Harry Brooks
Minneapolis, Minn.

Mrs. Leona Mutch
Minneapolis, Minn.

Memorial contributions are a practical means of honoring the memory of a friend or loved one, while helping the Minnesota Medical Foundation in the advancement of medical education and research. Appropriate acknowledgements are promptly sent to both donor and family of the deceased.
Coming Events

University of Minnesota Medical School

List of Continuation Courses for Physicians
1960-1961
University of Minnesota
Center for Continuation Study

May 1-3 . . . . Ophthalmology for Specialists

May 8-10 . . . . Gynecology for General Physicians and Gynecologists

May 11-13 . . . . Surgery for Surgeons

May 15-19 . . . . Proctology for General Physicians

June 1-2 . . . . Psychiatric Emergencies in Medical Practice

1960-61 all year . . Cancer Detection for General Physicians

The University of Minnesota reserves the right to change this schedule without notification.

Courses are held at the Center for Continuation Study or the Mayo Memorial Auditorium on the campus of the University of Minnesota. Usual tuition fees are $30 for a two-day course, $50 for a three-day course, and $75 for a one-week course. These are subject to change under certain circumstances.

Specific announcements are sent out for each course to all members of the Minnesota State Medical Association and to any physicians who request information for a specific course, about six weeks to two months before the date of the course. For further information write to:

DIRECTOR
DEPT. OF CONTINUATION MEDICAL EDUCATION
1342 MAYO MEMORIAL
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINNESOTA
A Word About

Memorial Gifts

The Minnesota Medical Foundation welcomes your memorial contributions when an appropriate occasion arises. Memorial gifts serve the living and pay thoughtful tribute to the memory of a friend or relative.

The Foundation will promptly acknowledge your gifts to both the donor and the family of the deceased. The gift will help finance the Foundation's program for the advancement of medical education and research. The Medical School at the University of Minnesota will be the direct benefactor.

Gifts should be sent to the Minnesota Medical Foundation, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.