

Staff Meeting Bulletin  
Hospitals of the » » »  
University of Minnesota



Irradiation Leucopenia

STAFF MEETING BULLETIN  
HOSPITALS OF THE . . .  
UNIVERSITY OF MINNESOTA

Volume XVI

Friday, December 8, 1944

Number 8

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Published for the General Staff Meeting each  
week during the school year, October to May.

Financed by the Citizens Aid Society,  
Alumni and Friends.

William A. O'Brien

I.

## UNIVERSITY OF MINNESOTA MEDICAL SCHOOL

## CALENDAR OF EVENTS

No. 50

December 11 - December 16

Visitors Welcome

Monday, December 11

- 9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.
- 12:30 - 1:30 Pathology Seminar; Bone Marrow Studies; Sheldon H. Stuurmans; 104 I.A.

Tuesday, December 12

- 9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 11:00 - 12:00 Urology Conference; C. D. Creevy and Staff; Main 515, U. H.
- 12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff; 104 I. A.
- 12:30 - 1:30 Physiology-Pharmacology Seminar; The Intestinal Absorption of Water and Electrolytes; The Fluid-circuit Theory of Water and Electrolyte Absorption from the Intestine Applied to Isotopic Data; M. B. Visscher, 214 M. H.
- 4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Station 54, U. H.
- 4:00 - 5:00 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.
- 4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.
- 5:00 - 6:00 Roentgen Diagnosis Conference; A. T. Stenstrom, L. P. Anderson, 515 U. H.
- 8:00 - Recording Changes in the Living Body by Electronic Means; E. H. Wood, C. F. Code, E. J. Baldes, R. E. Jones; KSTP's New Theater Studio H in Radio City.

Wednesday, December 13

- 9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff; Station 60, Lounge, U. H.
- 11:00 - 12:00 Pathology-Medicine-Surgery Conference; Old Myocardial Infarct Mural Thrombus; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.
- 12:30 - 1:30 Pediatrics Seminar; The Radiology of Bone Tumors; L. G. Rigler; W-205 U. H.

- 12:30 - 1:30 Physiological Chemistry Literature Review; Staff; 116 M. H.
- 12:30 - 1:30 Pharmacology Seminar; Experimental Treatment of the Heart Worm of the Body; Dr. McManus; 105 M. H.
- 4:30 - 5:30 Neurophysiology Seminar; The Influence of Muscle Pain on the Motor Cortex; Josef M. Brozek; 214 M. H.

Thursday, December 14

- 9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 4:00 - 5:00 Physiological Pathology of Surgical Diseases; Physiology and Surgery Staffs; Todd Amphitheater, U. H.
- 4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.
- 4:30 - 5:30 Bacteriology Seminar; Coccidioidomycosis; Robert Omata; 214 M. H.
- 5:00 - 6:00 Roentgenology Seminar; Review of Recent Radiological Literature, M-515 U. H.

Friday, December 15

- 9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-214 U. H.
- 10:30 - ~~10:30~~ Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department.
- 1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff, Eustis Amphitheater, U. H.
- 1:00 - 2:30 Dermatology and Syphilology: Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U. H.
- 1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff; Todd Amphitheater, U. H.
- 4:30 - Lecture: Two Kinds of Thinking, Alan Gregg; Director for the Medical Sciences of the Rockefeller Foundation; 15 M. Sc.

Saturday, December 16

- 8:00 - 9:00 Surgery Journal Club; O. H. Wangenstein and Staff, M-515 U. H.
- 9:00 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff, W-205 U. H.
- 9:15 - 10:30 Surgery-Roentgenology Conference; O. H. Wangenstein, L. G. Rigler and Staff, Todd Amphitheater, U. H.
- 9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, M-515, U. H.
- 10:00 - 12:00 Medicine Case Presentation; C. J. Watson and Staff, M-515, U. H.

## II. IRRADIATION LEUCOPENIA

J. L. McKelvey

The Department of Obstetrics and Gynecology and the Division of Irradiation Therapy have been concerned for some time with the problem of leucopenia resulting from X-ray irradiation of pelvic malignancy. The department of Internal Medicine has been interested in certain aspects of the treatment of this and other forms of leucopenia. This is, then, a joint report on recent experiences. The object of the paper is to present these experiences, to evaluate the problem as it applies to Gynecology and to report upon attempts which have been made to treat the condition. The work is far from complete. The justification for presenting it at this time lies in the fact that the frequency and severity of irradiation leucopenia has been given little attention. The work of Sebrell has caused a flurry of interest in folic acid and has suggested that it may play a part in the normal mechanisms of the control of white blood cells. Experiences with this may be worth reporting.

A great deal of work has been done in studying the effect of irradiation upon white blood cells. The conclusions as to what happens have met fairly general agreement. No agreement has been reached as to the mechanism by which the effects are produced and most of the reasoning has been by exclusion. What is more important from the point of view of the present discussion is that little attention has been given to the pathological degree of leucopenia which is not infrequently seen in association with pelvic malignancy irradiation therapy and which may seriously interfere with the continuity or completion of this therapy and may even be occasionally fatal, particularly if it be not recognized in its early stages. And no reasonable solution of the problem of therapy of the leucopenia in these several grades has been suggested.

The difficulties of the interpretation of the reported studies might perhaps be pointed out before these studies are

considered in detail. A large part of the work has been done upon the rodent. The rat and mouse are notoriously poor animals for this field of investigation. They are small so that relatively enormous proportionate volume dosages of irradiation are almost inescapable. The mouse is reported to show striking differences in the numbers of white cells of blood removed from different portions of its body. The rat will show as much as 50% variation in the white blood count of peripheral blood when exposed only to emotional disturbances and this has led at least one investigator into gross error.

Various parts of the body have been irradiated. The results are strikingly dissimilar. Much of the work has been done upon animals who have been given total body irradiation and the information available at present would seem to support the conclusion that this has little in common with any part of the practical problem in the human. Single dosage has produced different effects from repeated soage. The variations in total dosage from small to massive doses has produced much less variation.

It is true that every cell has a measurable lethal dose of irradiation energy. But within the bounds of reasonable therapeutic dosage it is most inconvenient that the white blood cells can be scarcely influenced in vitro, even when tissue culture conditions are supplied.

Finally, it seems clear that individuals within a species may show peculiar effects upon white cells from interferences of one sort or another which do not measurably affect the majority of the species. One can think of this vaguely as a form of sensitization. It must be borne in mind in any consideration of severe leucopenias in both animals and man, and from the present point of view, must be considered in the interpretation of the more severe irradiation leucopenias.

### The White Blood Cells As A Group

Since the beginning of this century

it has been known that the exhibition of irradiation energy to the human brings about a drop in total white blood cells of the circulating blood and that the effect is usually roughly proportional to the amount of energy supplied and to the volume of tissue treated. The lymphocytes seem to be most rapidly and readily affected. The red blood cells are resistant. Further studies showed that it required from 6 to 8 weeks for recovery to take place. The proportion of lymphocytes to other white blood cells returns to normal well before total recovery is reached. During and shortly after the exhibition of irradiation energy, immature forms are found in the circulating blood.

Most investigators agree that following a small dose of X-ray there is a passing phase of leucocytosis. This has been attributed to stimulation of bone marrow, to toxic substances from disturbed cell metabolism, to absorption of tumor degeneration products, and to other things. In larger doses, there seems to be a drop in white blood cells which is immediate. With continuing irradiation, this drop reaches a base level and only some individuals of the group will go on to severe leucopenias.

There are various possible causes for this. The fact that reasonable doses will produce little effect on white blood cells in vitro does not entirely rule out a direct effect on the circulating white cells since the milieu in vitro is grossly abnormal even under tissue culture conditions. It does, however, strongly suggest that the leucopenia is due to another cause.

Zwerg irradiated the skulls of rabbits after protecting the underlying tissue from the irradiation. If the circulation to the irradiated tissue were cut off during and for four hours after the irradiation, no leucopenia developed. If the circulation was reestablished immediately after irradiation, a leucopenia developed. He concluded that the leucopenia was produced by the release of a toxic substance. It is odd that this should entirely disappear in four hours. The majority of investigators agree that the leucopenia is due to a toxic interference with bone

marrow and not to a direct effect on the circulating blood. This is supported by the occurrence of a leucopenia when irradiation is given in such a way that no bone marrow is exposed to it.

That something is disturbed in the bone marrow is evidenced by the appearance of immature white cells in the peripheral blood. There is, then, a shift to the left. Minot and Spurling studied the blood after irradiation of the head, neck, and chest. They reported the subsequent appearance of 3 to 5% of immature forms with a maximum of 10%. Myelocytes were not seen. This has been confirmed by Jagenow for treated genital carcinoma and by Heim for both small doses to the ovary and cancer doses to the pelvis.

The department's experience is somewhat limited. The appearance of immature forms has been confirmed but neither the time of their appearance nor their proportion has been found useful in prognosticating the onset or the degree of a severe leucopenia. Sternal puncture has been done in only three patients with severe leucopenia. Two of these were reported as hyperplastic with the picture of a metamyelocyte arrest. The other was hypoplastic.

### Lymphocytes

There is general agreement that the lymphocytes are more sensitive to change in association with irradiation than other white blood cells. Expressed in relative numbers, they drop more rapidly and return more rapidly than the other white cells. Regaud has studied this extensively. When a whole animal is irradiated with appropriate doses, the lymphocytes will disappear entirely after 5 to 6 days and remain absent for 2 to 3 days. If moderate doses are repeated the lymphocytes may continue to be absent until the animal dies. This is about what one would expect from a knowledge of the histological changes produced by irradiation in such glands as the thymus.

In the human, Seitz and Wintz showed that large single doses of X-ray always

produced a decrease in lymphocytes in 3 days. After 6 weeks, 62% had returned to normal, 13% remained below normal, and 25% were above the pre-irradiation values. They claim, however, that the change is relatively small with single dose pelvic carcinoma therapy. An average value of 28% dropped to 25 to 26% after 5 days and after 8 to 12 weeks had reached 30%. There is considerable argument as to the mechanism by which this is brought about.

The local experiences confirm without question that a drop in lymphocytes does occur with irradiation. It is usually but not always proportionately slightly greater than the drop in other white cells but only very rarely reaches dangerous levels. X-ray therapy is stopped if the lymphocytes decrease to 7%. This is occasionally useful as an indication of a very acute irradiation damage and may occur before other evidence is available. That it does not always occur is evidenced by the fact that the average of the lowest recorded lymphocyte counts for the group of leucopenias considered here was 31%. The lowest individual finding, however, was 13%.

#### Polymorphonuclear Leucocytes

In response to irradiation, the polymorphonuclear leucocytes behave somewhat differently than the lymphocytes. With a single large dose of irradiation, there is an early rise in the numbers in the circulating blood, followed by a drop which is neither so rapid nor proportionately so large as the drop in lymphocytes. Regaud studied animals given total irradiation. He reported that the polymorphonuclear leucocytes in the bone marrow are rapidly thrown into the general circulation so that they may nearly disappear from the bone marrow. This seems to have a questionable relation to the events which occur in the human with localized therapy.

#### Eosinophils

There is some eosinophilia in the presence of a cancer but this is not striking. There is usually some increase in eosinophils late in the course of the

recovery from irradiation. It has been reported that a local eosinophil infiltration into a cancer, particularly after irradiation, suggests a somewhat better prognosis than the average but this is open to question.

It is astonishing to find that attention has been focused upon these details of white cell response to irradiation while little or nothing has been written of the practical problem of the severe grades of the condition. It can only be assumed that the problem is confusing and has not yielded conclusive results to study.

#### Material

In order to obtain a more accurate expression of our own material, 100 case histories were chosen at random. These were records of patients who had been treated for carcinomas and all had had irradiation. All were treated during the past five years and during this time the therapy has been standardized. They are hospitalized throughout treatment. Very nearly exactly 3000 tissue roentgens is delivered to the cervix and this is given over about 30 days when no interference arises. The numbers and sizes of portals are determined to deliver a diffuse dose to the pelvis. Treatments are given daily except on Sundays and holidays. This is followed immediately by the introduction of radium which is given over 100 hours. Two intrauterine portals in tandem and three intravaginal portals are used when space permits. The dosage is usually about 4500 to 5000 mgm. hrs. but varies somewhat with the number of portals which can be used and with the characteristics of the tumor. The main dependence for therapeutic effect is placed upon the X-ray. Radium is used for an additional dosage to depth. The details of this do not concern us here.

This is a large dose and while it has justified itself in terms of results, it necessitates extremely careful handling of the patient receiving it. Careful control of the white blood cell counts is an essential part of the handling and a mass of carefully obtained

data is available

### Results

Over a 5-year period approximately 300 reportable (without previous treatment) carcinomas of the cervix were treated. In this time two patients died with leucopenia following irradiation. Neither of these turned up in the 100 case records taken at random. They are presented heresimply to demonstrate the type of damage which can occur.

The first patient was 37 years old and was about 4 months pregnant. She had a League of Nations stage I squamous cell carcinoma of the cervix. Her white blood cell count before treatment was 9700. On the 9th day of X-ray treatment this had dropped to 4200. Toward the end of therapy there was a low of 2050, but on the last day of X-ray therapy she had 3650 white blood cells. The vaginal portion of her radium was given immediately and 36 hours later she aborted spontaneously. Her post abortum course was febrile in spite of sulfadiazine. Unfortunately, no white counts were done during this time. On the 54th day after the beginning of X-ray her white count was 1900. Two days later it was 600; the following day 650, and from that day on it varied between 300 and 100. The patient died on the 63rd day after the beginning of X-ray. Autopsy showed a hemorrhagic pneumonia, bronchiectasis, and extensive ulceration of the stomach. The use of sulfadiazine may have played a part in the leucopenia.

The second patient was 58 years old and had a squamous cell carcinoma of the cervix, League of Nations stage II. Her white blood count was 14600 on admission. By the 14th day after beginning X-ray it had dropped to 5500 and it continued about this level. On the 25th day and before the completion of the X-ray a toxic erythema developed. The white count rapidly fell to 1200 on the 32nd day and 500 on the 33rd day when the patient expired.

It is evident then from these two cases as from others to be shown that there is a marked reduction in white cells in the circulating blood which may occur early in the course of X-ray irradiation

to the pelvis. These two cases demonstrate that occasionally this may proceed to extensive white cell loss with a fatal issue.

For consideration of the other 100 cases chosen at random, it became necessary to set up an arbitrary definition of the term leucopenia. The standard which was chosen was the occurrence of white blood counts below 3000 on more than one occasion. An occasional patient was excluded who had more than one drop below this level but who had counts before and after the low determination which were well above this level. The counts were almost always done early in the morning shortly after breakfast.

It was surprising to find that of the 100 sampled cases, 24 fell by these criteria into the leucopenic group. The majority of these showed persistence of the low count to the end of X-ray therapy although in a few it was intermittent. By various subterfuges such as postponing X-ray treatment, treating at intervals, or interjecting radium treatment, it was possible to complete the X-ray therapy in all but 2 patients though extension of treatment over 62, 60, 59, 55, and 52 days was required for 5 of the patients.

Further evidence of the effect of the irradiation upon the white cell count may be obtained from the non-leucopenic group. For these, the average admitting count was 8961. The average of the lowest single count for each patient was 3886. It may or may not be significant that the group which developed a leucopenia had an average admitting count of 6958 or 2000 less than the average for the non-leucopenics. The average lowest count for the leucopenics was 2115. The lowest single count in the group was 1200.

The appearance of the lowest count in both groups was usually after the 20th day of X-ray treatment. In some cases this occurred earlier, however, so that one cannot count upon freedom from danger in even the early days of



treatment.

Following the completion of this type of X-ray therapy there is a quite irregular recovery of white cells. There are not enough prolonged observations to justify a dogmatic statement as to ultimate effect. There have, however, been a number of patients who have been found to show a persistence of white counts between 3000 and 4000 for long periods of time. One patient who had an admitting count of 10800 and a low during therapy of 5400 on the 8th day of this therapy, had white counts of 3100 after 5 weeks, 3500 after 7 months, and 3790 after 4 years. There is no evidence as to the ultimate fate of these. Most counts return irregularly to normal but this is grossly irregular by comparison with the experimental evidence of a return to the status quo ante at 6 to 8 weeks.

There is not sufficient reliable information in this series to justify conclusions as to the clinical significance of the appearance of immature forms of white cells in the peripheral blood. This has been demonstrated to occur but so far as can be determined at present, it is not of prognostic value and does not appear to be related to the severity of the disturbance of numbers of the circulating white cells. Further study is required before anything resembling a conclusive statement can be made.

A somewhat similar statement may be made for the lymphocyte counts. The average of the lowest single counts of the leucopenic group was 24%. Single lows of 13, 16, 19, and 20 were observed. There is no question but that the lymphocyte count drops on the exhibition of this form of irradiation and that the loss is somewhat earlier than that of the other white cells. From a practical point of view the problem seems to concern rather the individual patient with an exaggerated response than the group. One looks upon such a severe and sudden drop in the proportion of lymphocytes as evidence of a dangerous acute damage. In our hands, it has proven clinically safe to continue therapy until a 7% lymphocyte count is reached. Recovery may be counted upon, other factors being equal. Such

drops are rare.

#### Treatment

It is clear that humans as well as animals may be destroyed by irradiation. The mechanism of destruction will vary with obvious factors. In the practical application of irradiation therapy one must count upon the fact that the mechanisms of the production of white blood cells are extremely sensitive to irradiation. The degree of the effect is loosely related to the area irradiated and the volume dosage. Within reasonable limits of volume dosage, 75% of patients seem to preserve adequate production of white blood cells. The 25% who show a leucopenia seem to manifest an abnormal sensitivity. It seems reasonably certain that those who suffer really severe damage to white cell production are hypersensitive individuals. The fault lies, then, in the tissue response of the patient. Since a response which may be termed leucopenia is of frequent occurrence and since it is reasonable to assume from experimental evidence that further irradiation will destroy a considerable proportion of these individuals with a clinical picture resembling agranulocytosis, it becomes obvious that certain controls and checks must be set up. These will represent only a prophylaxis against possible destruction of the patient. On the other hand there is the fact that the patient has a malignant disease which will destroy him unless adequate treatment can be given. Occasionally, a surgical attack represents a possible alternative to irradiation. In so far as cervical carcinoma is concerned this represents most often either a second best choice or an impossibility. To stop treatment over long periods of time is no adequate solution since variation of the time factor disturbs the biological effects of the irradiation beyond present ability to calculate it. The relative recovery rates of tumor and normal tissue are such that prolongation may spoil the differential sensitivity upon which the value of irradiation rests. Prophylaxis which is designed to prevent destruction by the irradiation is not the only feature for

consideration. Active treatment of the leucopenia in order that irradiation may be continued to prevent destruction by the tumor is equally important. It is this which has concerned the department recently.

### Prophylaxis

There is no known method of preventing the original drop in white blood cells which occurs with the institution of irradiation therapy to the pelvis. Prophylaxis then, is aimed at the recognition of serious drops in order that the irradiation may be stopped and active measures, so far as they are available, be instituted. Again, certain dogmatic standards must be set up. The significance of sudden and severe drops in the proportion of lymphocytes has been mentioned. It was stated that irradiation is stopped when this reaches 7%. This is a rare occurrence.

The speed of the drop is significant. Precipitous drops will justify stopping therapy for observation of the base level. When the drop is slower, therapy may be continued cautiously until the count reaches 2000 although the Division of Radiation Therapy here has preferred to be somewhat more cautious.

White cell counts done twice a week are probably sufficient so long as the count remains above 4000. When lower levels are found, daily counts are done and treatment is not given until that day's finding is reported. The white counts should be done in so far as possible under standard conditions of time of day, relation to food intake, and exercise.

If X-ray be stopped early enough, serious damage is unlikely. Recovery, measured in terms of the numbers of white cells, is, however, small and slow. For this reason, again, some form of active therapy is desirable.

### Therapy of Irradiation Leucopenia

Various forms of therapy have been suggested. It is enough for the purposes of this paper to simply say that they have proven almost completely ineffective in

the department's experience. This is true of large intravenous doses of vitamin C, of pentonucleotide, and blood transfusions. Pentonucleotide has the added disadvantage of making a considerable proportion of the patients to whom it is exhibited, severely sick.

Large doses of crude liver extract, folic acid concentrates and, interestingly enough, the application of intra-uterine and vaginal radium all seem to be more or less effective in raising the white blood count. Unfortunately, these are temporary elevations but are of an order which have made them useful in continuing therapy. The fairly rapid subsequent drop suggests that the effect is limited to a release of white cells from some source. There is still too little evidence to support the conclusion that leucocytopoiesis is significantly affected.

The effect of the introduction of radium is startling. It is one of the few real evidences of the efficacy of treatment with "a hair of the dog which bit you." Of the 24 patients of the leucopenia group, there are useful observations on 11. The last white counts before the introduction of radium were compared with the maximum count of the elevation. In every patient but one a significant rise was encountered. The one patient had a count of 5300 before radium was applied and a maximum of 5900 thereafter. The average count before radium application was 3023 and the average maximum following it was 5659. The elevations of white count were not long maintained but on occasion were useful. It is inconceivable that this is due to the gamma irradiation and observations are now being undertaken to investigate the effect of simple mild trauma to the region of the tumor.

There has been made available recently to the Departments of Obstetrics and Gynecology, and of Internal Medicine, a concentrate of folic acid for clinical trial. The name folic acid was apparently suggested by Mitchell, Snell, and Williams<sup>1</sup> in 1941. It has been obtained from liver and spinach and an apparently similar substance may be derived from

grass and yeast. It is apparently identical with the material described as vitamin B<sub>9</sub> (B sub C). In 1942, Spicer, Daft, Sebrell, and Ashburn<sup>2</sup> published a report which showed that rats which had been made agranulocytic by the feeding of whole dried liver and "certain liver concentrates." The same material prevented the development of the agranulocytosis. In both cases the sulfonamide therapy was continued during the liver feeding. In 1943, Daft and Sebrell<sup>3</sup> reported their findings in the treatment of this condition in rats with folic acid concentrates. Comparable results were obtained and they concluded that folic acid is the active anti-agranulocytic factor of liver. A considerable amount of work has been done with folic acid. References to some of this may be obtained from the papers quoted.

Folic acid was not at first available. On the advice of Dr. C. J. Watson, older and less concentrated forms of liver extract were used. The Lederle 3 cc. ampoule was used. Information was not available and indeed is not yet available as to desirable dosages for this condition for the human. Nor was it known what amount of folic acid was available in the liver extract which was used. Eli Lilly claims that their 15 unit ampoule (No. 354) contains roughly 10.5 micrograms of folic acid per cc. and their No. 343 powder contains about 24.4 micrograms per gram. Daft and Sebrell had fed their rats dosages of 10 and 20 micrograms of folic acid (per day or total dose?). It was obvious that proportionate amounts could not be obtained for the human from the available supply of liver extract. However, some result was obtained and this will be demonstrated with slides.

Through the kindness of the Lederle Laboratories who manufactured the material, and of Dr. Sebrell who made it available, it was possible to clinically test the folic acid in the form of a concentrate, and in one patient, in crystalline form. As the concentrate 2.75 mgm. of folic acid was given twice a day for approximately 5 days.

There are not enough patients in either

the folic acid or the liver extract group to be conclusive. The results in 5 patients who were given folic acid during X-ray therapy and in a 6th who received it later are being demonstrated in slides. Only two records of patients who received liver extract during therapy turned up in the random sample. These will serve our purposes until more accurate information is available and the results will be demonstrated in slides.

#### Liver Extract

., 49 years. Squamous cell carcinoma of the cervix, League of Nations stage I. This patient entered the hospital with a severe anemia (Hbg. 78 gm.) due to blood loss. Her white blood cell count on admission was 4700 and 6 days later was 4450. X-ray was started at once and two blood transfusions were given. On the 13th day after the beginning of X-ray therapy the white blood cells had fallen to 1200 and on the following day a count of 2000 was obtained. Liver extract, 3 cc. intramuscularly, was given on each of four successive days. X-ray therapy was continued daily.

<u>Day after beginning of liver extract</u>	<u>White blood cells</u>
1	3400
2	3500
5	3800
8	4600
9	2800
11	2700
13	3000

Therapy was completed without difficulty.

., 40 years. Squamous cell carcinoma of the cervix, League of Nations stage II. This patient entered the hospital with a white cell count of 5100. X-ray was begun at once. By the 9th day of treatment, the count had fallen to 2400. It remained about 2500 without further X-ray to the 19th day when intrauterine and vaginal radium was applied. During this radium therapy, the count rose to 4300. Multiple

attempts at X-ray were made but the count dropped to reach 1200 on the 39th day after beginning of X-ray therapy. Liver extract, 3 cc. intramuscularly, was given daily and later at short intervals until 156 cc. had been given. Very little response was obtained and the X-ray therapy was never completed. A total of 2100 tissue roentgens was given to the cervix over a total of 59 days.

A third patient ( ) received both liver extract and folic acid. There was no demonstrable response to the liver extract although it was given over 16 days.

### Folic Acid

The responses to folic acid are much more readily demonstrated by graphic means in the accompanying slides. A brief resume' is given here for the purpose of completing the record. Four patients received folic acid and continuous X-ray therapy. Two of these each had two courses of folic acid. One of these had one course of intravenous crystalline folic acid. The remainder received a concentrate containing 2.75 mgm. of folic acid twice a day for 5 days with the exception of one who received a similar dosage for 8 days. The average white cell count at the beginning of therapy was 2175 and the average maximum response to therapy was 4175. There was a response in terms of an elevated white cell count in every instance but one. In this case, the patient received intravenous crystalline folic acid with a poor response. After an interval of 4 days, the concentrate was given by mouth without demonstrable effect.

Two further patients were treated with folic acid. One was readmitted to the Internal Medical service a month after completion of her therapy because of an ulcerative colitis which was probably an irradiation factitial proctitis. X-ray therapy had been associated with a leucopenia although treatment was completed. Seventy-six days after completion of the X-ray her white cell count was 3600 and folic acid concentrate was given by mouth. The white count rose to 5650 on the 4th day of folic acid therapy and had re-

turned to 3600 on the 9th day. Thirteen days after beginning the first folic acid therapy a second course was begun. An original white cell count of 3200 rose to 4700 on the 6th day after beginning this treatment and was still 4000 on the 11th day.

One other patient was treated with folic acid which was given during the last 3 days of X-ray treatment and the first 2 days of radium. A beginning white cell count of 2600 rose to 7800 on the 6th day and fell to 3650 on the 12th day. Five months later the white cell count was 3700. It was unfortunate that folic acid and radium were used concurrently here.

Significant elevation of white cells begins 4 to 5 days after the onset of folic acid administration. The effect of a 5 day therapy lasts for 7 to 14 days. There has been no experience with prolonged therapy.

The details of the case records will be published shortly. It must only be stressed at present that while the results are suggestive, no conclusions should be drawn until further observations have been recorded. There is no certainty of the mechanism by which folic acid produces its effect. The material is not commercially available and the present methods of production make it much too expensive for other than investigative use.

\* \* \* \* \*

The Department of Obstetrics would like to express its appreciation for help and coopeation in this work to Dr. C. J. Watson and Dr. W. K. Stenstrom, to Dr. W. H. Sebrell of the U. S. Public Health Service for obtaining the folic acid for use, and to the Lederle Laboratories, Inc., for supplying it.

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2. Spicer, S.S., Daft, F.S., Sebrell, W.H., and Ashburn, L.L. - Public Health Rpts., Vol. 57, No. 42:1559, '42.
3. Daft, F.S., & Sebrell, W.H. - Public Health Rpts. Vol. 58, No. 42:1542, '43.

### III. GOSSIP

Deborah MacLurg Jensen, Washington University, St. Louis, is teaching the course in ward administration for nurses at the Center for Continuation Study this week. She will be remembered as a former nurse in this school and the wife of Julius Jensen, who was here in the department of Medicine some years ago. His contributions on the heart in pregnancy are well known...Coffee hour for sophomore students and medical school faculty was a success. A few weeks ago the Freshmen and staff had a get-together, and similar meetings are planned for Juniors and for the Seniors. Chief items of interest for discussion are socialized medicine and the examination system.... Burtrum C. Schiele of the department of Neuropsychiatry visited the Station Hospital in Fort Des Moines this week on War-time Graduate Medical Meetings assignment. Speaker has the entire group in the afternoon, and after mess those particularly interested gather for a bull session.... Radiologist, Leo G. Rigler, is making his second visit to Schick General Hospital, Clinton, Iowa, for War-time Graduate Meeting this week....Peter Ward, Superintendent, Charles T. Miller Hospital, St. Paul, has been named President-elect of the American Hospital Association. 100 friends gathered in the Radisson Hotel to honor him at a special dinner December 6. Dr. Ward occupies a prominent place in state and national hospital circles....Plans for continuation study courses and fellowship training for returning service physicians are developing rapidly. At present time 82% of A.M.A. physicians answering questionnaire indicated a desire for short or long course (24% short, 58% long, 18% none). Short course preferences in order are Internal Medicine, Surgery, Obstetrics and Gynecology, General, and Pediatrics. Long course group ranking is: Surgery, Internal Medicine, Obstetrics and Gynecology, General, Psychiatry and Neurology. These figures differ from those compiled by Minnesota State Medical Association. In the blank issued by the American Medical Association there is a space for the officer to indicate which institution he would like to attend. It is obvious that unless some plan for providing teaching material can be evolved that the program will fail. It is probable that financing

the staff will not be as difficult as getting the material....Interest in the disease, alcoholism, continues to grow. In spite of efforts to the contrary, most alcohol education tends to deviate from a factual approach. An analysis has been made of the educational literature in this field, and much loose thinking and writing has been discovered. Center of interest in this country is at Yale.... Public Health has brought about another change in our way of life. Funerals today are largely conducted on older individuals. Grief is tempered by common sense and cost studies reveal changes in our way of thinking about services for the departed. Funeral directors are often blamed for excessive costs when actually they have tried to prevent the family from spending so much. For many people, it is the opportunity of a "lifetime," to be important. Failure to recognize the funeral director and embalmer as a social factor often leads to difficulty in obtaining postmortem examinations. A few years ago an elderly man called to make arrangements to have his body sent to Anatomy. He had a small amount of money which he preferred to give to a character building organization for boys rather than to use it for his own funeral (one of the few examples of real unselfishness I have seen)....The hours of sunshine are growing longer and Christmas will soon be here. I attended a conference of the American Legion last week and learned of their plan to give gifts to service men. They should be sent to Legion headquarters and must vary in price from one to five dollars only. Name of article, price, name of donor, should be attached to wrapped packages. In distributing packages all men in the ward will obtain gifts of approximately the same cost and character. The pile of packages at headquarters is enormous. American Legion Auxiliary is one of the most powerful social groups today. As far as I know they are the only women who do what their husbands tell them to do. They were advised on many things, but especially to urge returning veterans to go to school instead of taking an easy job, and also on the importance of exhausting every means of rehabilitating the N.P.'s before paying them for being sick.....