Acute Medical Disorders

DIAGNOSIS AND TREATMENT

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By: Francis D. Murphy, M.D., F. A. C. P., Professor and Head of the Department of Medicine, Marquette University School of Medicine; Clinical Director of the Milwaukee County General Hospital and Emergency Unit.

510 Pages Illustrated $6.00

F. A. DAVIS COMPANY 1914 - 16 CHERRY ST.
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New Developments in Antisyphilitic Therapy

Edwin H. Cressman

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Lymphatic Leukemia: A Case Report with Autopsy Findings

William Baldwin, Jr.

Published monthly by the
PHILADELPHIA COLLEGE OF OSTEOPATHY
48th and Spruce Streets, Philadelphia 39, Pa., U.S.A.
NEW DEVELOPMENTS IN ANTISYPHILITIC THERAPY

EDWIN H. CRESSMAN
Professor of Dermatology and Syphilology

Introduction

Will syphilis succumb to the onslaught of modern medicine? Through the years this disease has pursued its insidious, stubborn way, devastating the minds and bodies of its poor victims. Its swath of devastation has dwarfed the greatest of epidemics and world conflicts. Its destruction is not sporadic but continues from month to month and year to year without abatement. The day will come when this dread disease will suffer the fate of many another great plague, such as smallpox and diphtheria, but it will not be as easy. In controlling communicable disease we think of quick, sure diagnosis, segregation until the danger is over, a rapid and certain cure, and that which has been most successful, artificial immunization.

Historical Summary

Up to the present time we have only had the quick, sure diagnosis. The serologic tests have given us this. Their success or failure is in direct proportion to the frequency of their use. They can find syphilis, but what then? Can the patient be segregated until the danger is over? Segregation is impossible except for a small group. Can the disease be rapidly and certainly cured? Perhaps. This hope has been existent since Ehrlich’s discovery of arsphenamine in 1909. Artificial immunization is usually the most successful method of attack on communicable disease, but there is little hope of this for syphilis. Unfortunately syphilis is primarily a venereal disease, which complicates the problem in manifold ways.

To understand the trend of new research in the treatment of syphilis a brief recapitulation is worthwhile. In 1909 when Ehrlich synthesized arsphenamine he performed a chemical miracle. Highly poisonous arsenic had a high affinity for body cells, and a low affinity for the spirochete of syphilis. Ehrlich succeeded in reversing this effect. His new compound, arsphenamine, was strongly parasitotropic, and only weakly organotropic. Doses large enough to kill the organism could be introduced into the blood without great danger to the patient. Ehrlich believed he had discovered the "therapia sterilisans magna". The effects of the new drug were spectacular. Chancres and eruptions rapidly disappeared, usually after a single injection. This was indeed a medical triumph over the ineffectual mercury therapy of previous years. But it was not long before it was realized that very few of these patients were completely cured. There were numerous
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symptomatic relapses, and many cases of late syphilis developed. Then the treatment plan was intensified, taking a trend somewhat similar to some of the modern plans of intensification. Daily injections of arsphenamine were used for three successive days in the intensified plan of Politzer which was much in vogue. This was often repeated after a period of 6 to 8 weeks of mercury. Others gave daily injections of arsphenamine for 4, 5 or 6 days, etc. There were many plans. Arsphenamine in these plans of intensive dosage were found to be too dangerous, and the percentage of cures was not high enough, although the immediate clinical results in early syphilis were spectacular.

Later, Stokes, writing in 1926, made this comment: "A modern critic of such schemes of treatment* must, of course, point out that from the standpoint of curative effect, the wearing out of the infection is often possible where the effort to crush it at the start may fail." Gradually there evolved longer plans and more conservative dosage. In view of the earlier work, it is interesting to note that in 1944 we read of 332 cases of early syphilis treated with old arsphenamine given daily for 5 to 6 days. In this work the conclusion was reached that the plan was ineffective, dangerous, expensive, and altogether impractical. It would seem that this was discovered more than 20 years before by others.

In evaluating any new syphilotherapy the following questions must be considered: (1) Is it more effective? (2) Is it less dangerous? (3) Is it less expensive? (4) Is it simplified (easier for the patient, or easier for the physician)? (5) In addition to these criteria, it must further be remembered that the success of any plan can be determined only after many years of observing treated patients.

For some years the treatment of syphilis has followed a conservative plan in most cases. In early syphilis about 1 1/2 years of this form of treatment was needed. In some forms of late syphilis a much longer period is required. In these plans treatment danger has been reduced, and in early syphilis the rate of cure has been high. The results in late syphilis have been reasonably good, considering the fact that many of these advanced forms are irreversible pathologies.

In 1933 Leifer, Chargin, and Hyman initiated a vast amount of investigation. Once started, research gained tremendous momentum. Once again there has been a revival of the search for some plan approaching the "therapia sterilisans magna" of Ehrlich—a modern massive arsenotherapy. New drugs were tried—neoaarsphenamine, mapharsen and others. Neoaarsphenamine in intensive dosage was found to be more dangerous than mapharsen, and was discarded in favor of the latter.

New methods of administration were tried. It was thought that the intravenous drip method would reduce the drug danger of massive dose therapy. This is doubted now, and it is probable that the more convenient syringe technique is not more dangerous if the same dosage is used.

* Intensified plans using daily injections of arsphenamine.

Fever therapy combined with the various drugs was tried, hoping that it would reduce the drug danger, or increase the curability, or do both. In these intensive plans fever was used daily, and at various other intervals. Fever seemed to add something to the effectiveness of treatment, and while it did not diminish the toxicity of the arsphenamines if the same dosage was used, as good results could be obtained with smaller doses of the drug, and so the danger was reduced. Fever was induced in various ways, by malaria, by cabinet, by blanket, and by typhoid vaccine. The simplest plan is by the injection of typhoid vaccine.

Various durations of intensive therapy were tried, varying from 1 to 20 days. As might be expected the drug danger was greatly increased, particularly the more serious, and sometimes fatal, reactions of encephalopathy and agranulocytosis. While the search for a short, quick cure continued, investigation also took another direction. Drugs were given less often than in the intensive plans, and for longer periods of time—30 days, 8 weeks, 12 weeks, 26 weeks, thus constituting semi-intensive plans of therapy. Perhaps in the final analysis none of these plans of massive arsenotherapy will be permanently adopted as a routine for early syphilis. Yet even if this proves to be the case, a great deal of credit is due those men who aroused the renewed interest in a search for shorter and better methods of syphilotherapy.

Pertinent Research Findings in Intensive Therapy

From the literature on intensive therapy much can be gleaned which is valuable not only for the intensive plans for early syphilis, but also for the management of syphilis treated under conservative plans, and in other stages. The following is a brief summary of some of the more important facts.

Mapharsen Preferred

The arsphenamine of choice in any of the intensified plans of therapy now in use is mapharsen. The difference in toxicity between neoaarsphenamine and mapharsen when used in the weekly injection method of conservative treatment is only very slightly in favor of mapharsen. But the toxic ratio changes greatly in favor of mapharsen when the drugs are used in intensive and semi-intensive plans. At the present time no other arsphenamine should be used for this purpose.

Dosage of Mapharsen

The dosage of mapharsen under any plan of treatment should be governed by the weight of the patient, and not by an arbitrary dosage according to sex, as was customary practice. The individual dose should not exceed 1 mgm. per kgm. of body weight in any intensive plan of treatment. In all plans for the treatment of early syphilis the approximate individual dose should be based on these figures.
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In the therapy of early syphilis the greater the size of the individual dose the greater the therapeutic effectiveness. Contrary to what one might believe, the interval between doses in massive therapy is not so important. Much more important is the total amount given throughout the entire treatment period. It seems quite evident that the total amount given has a direct relation to the therapeutic effectiveness. The total curative dose for intensive and semi-intensive plans of therapy is from 20 to 30 mgm. per kgm. of body weight, giving total dosages of from 1200 to 1500 mgm. The total curative dose for the weekly conservative plan of treatment should be somewhat higher, from 30 mgm. to 40 mgm. per kgm. of body weight, or a total dosage of from 1600 to 2400 mgm.

**Efficacy of Intensive Therapy**

Intensification does not increase the therapeutic efficacy. It now seems apparent that the conservative plan of weekly injections offers as high a ratio of cures as can be attained by any intensive or semi-intensive plan. When the various systems are properly managed, comparable results are obtained.

**Risk of Intensive Therapy**

Intensification of therapy increases the drug risk in direct proportion to the degree of intensification. In other words, the shorter the treatment period the greater the drug danger, if the treatment plan is to produce comparable results. It seems highly likely that at the present time there is no plan completed in less than 20 days which gives a sufficient margin of safety.

**Methods of Administration**

The methods used for administering the drug have been slow intravenous drip, rapid intravenous drip, and multiple injections by syringe. In the beginning it was believed that the slow intravenous method would permit the administration of large doses repeated daily without great drug danger. This does not seem to be the case with arsenical drugs in the treatment of syphilis. Drug reaction is in proportion to the size of the dose, and the frequency of administration. In other words, if the same dose is given and repeated at the same time interval, there is no difference in the number of toxic reactions whether it be administered by slow drip, rapid drip, or by syringe. Since the syringe method is simpler, it should now be the method of choice.

**Antidote for Arsenamine**

If massive dose therapy is ever to become routine it must be made safer. For many years there has been a search for an antidote which might be combined with the arsenamine drugs in the treatment of syphilis. Such an antidote, if found, might be administered coincidentally and would make it possible to administer larger doses with greater safety. At present nothing which has been tried has proven effective in reducing the toxicity of these drugs.

**Dosage in Secondary Syphilis**

In order to obtain the same rate of cure secondary syphilis requires larger arsenical dosage than does primary syphilis.

**Serologic Tests in Intensive Therapy**

In a review of quantitative serologic studies in the treatment of early syphilis by the intensive plans of therapy some interesting and perhaps valuable, information can be obtained. The serologic tests remain positive for a variable length of time after intensive therapy. During this time the serologic titre is gradually falling. In general, the earlier a patient starts treatment the sooner the serum becomes negative. Patients with a lower titre at the beginning of treatment have better results than those with a higher titre. It has been suggested that patients may be treated by greater or lesser total dosage of arsenicals depending upon the character of the titre response. At the present time titre estimation is not part of the routine treatment of syphilis, but is under study by many clinics. It may be possible that titre estimation before and during treatment may be of value in judging the progress of the case.

Under any of the intensive or semi-intensive plans of treatment the patient should be examined, and a blood serologic test should be done monthly for 6 months, and repeated in the ninth and twelfth month after the completion of treatment. The spinal fluid should be examined during the period between the sixth and the twelfth months after completion of treatment. After this the patient should have the conventional bi-annual observation for a period of 5 years.

**Combined Drug Therapy**

It has been demonstrated that the combined use of arsphenamines and bismuth given at one and the same time has an additive and synergistic effect. The spirillicidal and curative effects of the two drugs when used at the same time are greater than when either of the drugs is used individually. Furthermore, this does not increase the drug danger. If desired the drug danger in combined arsphenamine-bismuth treatment can actually be reduced by reducing the dose of the arsenical without sacrificing therapeutic efficacy. This plan of combined drug therapy is not new. It is particularly applicable in the treatment of early syphilis. It should be used in all plans, whether intensive, semi-intensive or conservative.

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seems logical that the danger of this therapy can be lessened by reducing the dosage of mapharsen, and combining it with some form of fever therapy. The trend at present seems to favor 2 or 3 prolonged, high fevers, in the cause of treatment.

Conservative Therapy for Early Syphilis

The conservative plan of therapy in which weekly doses of arsphenamine and bismuth are administered for a period of approximately 1½ years has not been replaced by any of the intensive or semi-intensive plans. With the conservative plan of therapy there is less drug risk. A 5-day treatment plan, for instance, has a drug risk approximately 100 to 200 times greater. Other plans of therapy carry a drug risk in direct proportion to the length of the period of treatment. It is also evident that the conservative plan of therapy, if properly managed, has a cure rate as good or better than any of the massive dose plans yet introduced.

Mapharsen Preferred

While mapharsen is the drug of choice at the present time, it should be noted that the difference between neoarsphenamine and mapharsen in reaction incidence, when used in the weekly injection plan, is very slight. The two drugs can be used interchangeably, with a slight preference for mapharsen. If reactions occur with one drug a change can be made to the other, and at times the reactions will be avoided. Newer drugs, such as phenarsine hydrochloride and chlorarsen, may prove to be equally effective, but are too recent for accurate evaluation.

Dosage of Mapharsen

The older method of dosage according to sex (0.04 gm. for the female and 0.06 gm. of mapharsen for the male) should be discarded. The single weekly dose should approximate 1 mgm. per kgm. of body weight. The following dosage of mapharsen is suggested for both male and female:

- Under 110 pounds ................. 0.04 gm.
- 110 to 150 pounds .............. 0.04 or 0.05 gm.
- Above 153 pounds .............. 0.06 gm.

In using other arsenicals, dosage according to weight should also be employed.

Combined Drug Therapy

Bismuth is used in conjunction with mapharsen. Subsalicylate of bismuth suspended in oil is the preparation of choice because it permits the injection of a single weekly dose. Other preparations which are more rapidly absorbed must be injected more often. A standard preparation contains 0.13 gm. or 2 grains per cc. The following dosage of bismuth subsalicylate is recommended:

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Bismuth Subsalicylate Dosage</th>
</tr>
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<tr>
<td>Under 110 pounds</td>
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There is not the slightest doubt that great therapeutic advantage in the treatment of early syphilis is gained by using arsphenamine and bismuth as a combined therapy for 12 to 16 weeks at the beginning of treatment. Doses of each are given each week. The first 3 to 4 months are most important. Regularity of treatment is of utmost importance during this period if relapse, and neurosyphilis are to be prevented. The following is an outline of a plan we use:

12 weeks of mapharsen.
- Give bismuth subsalicylate the first 4 weeks, omit the next 4 weeks and give again during the last 4 weeks of this period.
- 4 weeks of bismuth alone.
- 10 weeks of mapharsen.
- Give bismuth the first 2 weeks and the last 2 weeks of this period.
- 6 weeks of bismuth.
- 10 weeks of mapharsen.
- 8 weeks of bismuth.
- 6 weeks of mapharsen.
- 14 weeks of bismuth.

Treatment is given for 70 weeks as outlined above, providing the blood serology becomes negative during the first 6 to 9 months and remains negative, and providing the spinal fluid examination is completely normal. Longer treatment plans are necessary in cases with persistant positive serology, serologic relapse, or nervous system invasion.

Serologic Tests During Conservative Therapy

The blood serology should be repeated every 3 or 4 months. Do not omit this because the blood becomes negative, serologic relapse can occur. The spinal fluid is examined any time after one year, but before completion of therapy. (Cell count, mastic or gold sol., globulin estimation, and the Kolmer complement fixation test are done.) After completion of treatment the blood serology should be watched for 2 or 3 years for possible relapse.

Indications and Plans for Intensive Therapy in Early Syphilis

Since the drug danger has not been reduced to a point where it compares with the safety of more conservative plans, and since no increased therapeutic effectiveness has been demonstrated for any reasonably safe plan, intensive therapy cannot be recommended for those who can and will pursue one of the longer, more conservative plans. But since early syphilis is a communicable disease all uncooperative patients should be hospitalized.
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There is not the slightest doubt that great therapeutic advantage in the treatment of early syphilis is gained by using arsphenamine and bismuth as a combined therapy for 12 to 16 weeks at the beginning of treatment. Doses of each are given each week. The first 3 to 4 months are most important. Regularity of treatment is of utmost importance during this period if relapse, and neurosyphilis are to be prevented. The following is an outline of a plan we use:

- 12 weeks of mapharsen.
  - Give bismuth subsalicylate the first 4 weeks, omit the next 4 weeks and give again during the last 4 weeks of this period.
  - 4 weeks of bismuth alone.
  - 10 weeks of mapharsen.
  - Give bismuth the first 2 weeks and the last 2 weeks of this period.
  - 6 weeks of bismuth.
  - 10 weeks of mapharsen.
  - 8 weeks of bismuth.
  - 6 weeks of mapharsen.
  - 14 weeks of bismuth.

Treatment is given for 70 weeks as outlined above, providing the blood serology becomes negative during the first 6 to 9 months and remains negative, and providing the spinal fluid examination is completely normal. Longer treatment plans are necessary in cases with persistant positive serology, serologic relapse, or nervous system invasion.

Serologic Tests During Conservative Therapy

The blood serology should be repeated every 3 or 4 months. Do not omit this because the blood becomes negative, serologic relapse can occur. The spinal fluid is examined any time after one year, but before completion of therapy. (Cell count, mastic or gold sol., globulin estimation, and the Kolmer complement fixation test are done.) After completion of treatment the blood serology should be watched for 2 or 3 years for possible relapse.

Indications and Plans for Intensive Therapy in Early Syphilis

Since the drug danger has not been reduced to a point where it compares with the safety of more conservative plans, and since no increased therapeutic effectiveness has been demonstrated for any reasonably safe plan, intensive therapy cannot be recommended for those who can and will pursue one of the longer, more conservative plans. But since early syphilis is a communicable disease all uncooperative patients should be hospitalized.
and treated by intensive methods. This should be accomplished by compulsion through the state health departments if it is to be successful.

Ten-Day Plan

Under these circumstances a plan of treatment covering 10 days as described by Thomas and Wexler, is one of the best. Daily injections of mapharsen by syringe are combined with bismuth, and fever is produced by the simple device of injecting typhoid vaccine. The daily dose of mapharsen for most patients is 0.06 gm. but the single doses should not exceed 1 mgm. per kgm. of body weight. Bismuth subsalicylate in doses of 0.1 gm. is injected on the first, third, seventh, and tenth days. Fevers are induced on the second, fourth, sixth, and eighth days by the intravenous injection of typhoid-paratyphoid vaccine. The initial injection is 0.1 cc., the second injection is 0.2 cc., the third 0.4 cc., and the fourth 0.6 cc. In order to induce the desired rise in temperature, it is usually necessary to repeat each dose in from 1½ to 2 hours. However, the dosage on each fever day is gauged by the febrile reaction produced. The amounts of vaccine suggested will usually cause a fever of 104° for about 4 hours.

Eight to Twelve-Week Plan

There are occasional circumstances which may make it desirable for some patients to choose some intensive plan of therapy. Under these conditions the patient should be advised of the increased risk before treatment. Hospitalization for one of the highly intensified plans is not desirable for this patient. With less risk, less expense, without bouts of high fever, and with the patient remaining ambulant, a moderately intensified plan of treatment can be completed in 8 to 12 weeks. Mapharsen is injected 3 times weekly until a total of 1500 mgm. is reached. The individual doses vary from 0.104 gm. to 0.06 gm. according to weight as stated previously. Once weekly an injection of 2 to 3 grains of bismuth subsalicylate is given, starting with the first injection of mapharsen.

Twenty-Six Week Plan

In July 1942 the U. S. Army adopted a plan of treatment which is consummated in 26 weeks. In this plan mapharsen is given twice weekly for 10 weeks, it is stopped for 6 weeks, then given again twice weekly for 10 weeks. Bismuth is injected once weekly during the first 5 weeks, then stopped for 5 weeks, then given alone for 6 weeks, stopped for 5 weeks, and given again during the last 5 weeks. With this plan effective therapy can be given with only slightly greater risk than in the conventional plan. The only patients who should be selected for this plan of treatment are those who, because of some circumstances, would probably not be able to complete a conservative routine.

Risk in Relation to Intensity of Therapy

As is indicated in the above data the risk becomes less as the plan of therapy is lengthened. In general, then, the indications for, or the choice of, a plan of therapy can be liberalized in direct proportion to the length of the plan, providing, of course, it offers equal therapeutic effectiveness.

Fever Therapy

In addition to the use of fever therapy in the treatment of early syphils already discussed, fever treatment is useful in the treatment of some forms of neurosyphilis, ocular syphilis, and probably in sero-resistant latent syphilis. Various forms of fever are in use today: malarial therapy, intravenous typhoid vaccine, and physical fever produced by the blanket method or by the cabinet method. The results of recent work would indicate that malarial therapy has no therapeutic advantage over fever artificially produced, and that in the treatment of syphilis, the results are definitely inferior if low temperature levels are employed. Temperature levels higher than 104° are necessary. The duration of the fever is also important. Longer periods of fever are more effective. This is particularly important in the treatment of neurosyphilis. Therapeutic effectiveness is probably increased when fever therapy and drug therapy are used concurrently.

Rapid Treatment of Neurosyphilis

Recently Dattner, Thomas, and Wexler have discussed a plan for the rapid treatment of neurosyphilis. Patients under this plan were hospitalized for malarial therapy. After the termination of the malaria, 10 daily injections of mapharsen were administered while the patient remained in the hospital. In a control group, patients were given malarial therapy followed by routine (prolonged) chemotherapy. Various forms of neurosyphilis were treated. In tabulating the results of these 2 plans of therapy, it was demonstrated that results obtained by the rapid method were as satisfactory as the results obtained with prolonged therapy.

The results of this plan proved again the effectiveness of fever therapy in the various forms of neurosyphilis. But more important, they indicate the possibility of an effective rapid form of therapy. A longer period of observation is necessary to judge the permanence of the results which were obtained.

Penicillin in the Treatment of Syphilis

Arsenotherapy was a tremendous stride in the control and treatment of syphilis. But in spite of their great effectiveness, the arsphenamines, both new and old, are dangerous drugs. Many have died, and many have suffered from drug reactions such as nausea and vomiting, dermatitis, hepatitis, encephalitis, etc., to say nothing of the excruciating pain, and
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NEW DEVELOPMENTS IN ANTI-SYPHILITIC THERAPY

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perhaps slough, caused by extravasation of the drug outside the vein. Bismuth was a comparatively harmless drug and added much to syphilitic therapy, but it did not have the punch necessary to cure a high percentage of cases of early syphilis. It was milder in action, and could only be used when combined with the arsphenamines, or in the treatment of pathologies which required mild therapy such as advanced cardio-vascular syphilis.

The next important advance in the chemotherapy of infectious diseases was the discovery of the sulfa group. These drugs, however, proved ineffective against the spirochete of syphilis. Now an antibacterial of most remarkable character, penicillin, virtually harmless to the human organism, and yet more potent in its peculiar way than the sulfa drugs, has been discovered. Could this drug have any value in the treatment of syphilis?

**Early Investigations**

John F. Mahoney of the U. S. Public Health Service, and Director of the Venereal Disease Research Laboratory at the U. S. Marine Hospital, Staten Island, N. Y., was destined to find out. He suspended the spirochetes of syphilis in a solution of penicillin and observed the result under the dark field microscope. One can imagine his emotions, realizing what this could mean, when he observed that penicillin had no effect whatever. The organisms were vigorously motile right in a concentrated solution of the drug. Here the investigation might have ended. To go further seemed useless. Nevertheless, animal experimentation was done, and strange as it may seem, spirochetocidal activity was demonstrated. This would seem paradoxical. It is certainly unexplainable.

The next step was to determine its usefulness in the treatment of human syphilis. Four cases of primary syphilis were selected for the first experiment. Each had a penile lesion with a positive dark field, and positive serology. Within the first 8 hours after penicillin therapy was begun the patients developed mild Herxheimer effects. The symptoms were headache, malaise, mild rise in fever, the penile lesions became painful, and the regional lymph glands became enlarged and tender. One patient had a mild secondary syphilid. These are reactions which occur the first day of the treatment with the arsphenamines, and are indicative of a marked effect of the drug upon the disease, probably spirochilidic. Furthermore, the spirochetes had disappeared from the penile lesions within 16 hours. The positive serology became negative in the usual length of time. Later Mahoney and his associates reported on a series of 100 cases of early syphilis treated with penicillin. There were some failures in this group, indicating the need for further study of time-dosage factors.

In the meantime a group of 23 cooperating clinics had been appointed by the Subcommittee on Venereal Diseases of the National Research Council to study penicillin in the treatment of syphilis, and to pool the results in an effort to determine the optimum method of using the drug. The preliminary report, on 1418 cases of early syphilis under treatment by this group describes the various dosage systems used, and the trial of penicillin combined with mapharsen. At the same time the action of penicillin on late syphilis is also being studied by this same group. From these and various other reports the following conclusions might be reached regarding the present status of penicillin in syphilis. It must be remembered that all of the reports are preliminary, the amount of work done is small, and as yet the period of observation is short.

**Penicillin Dosage**

The optimum time and dosage relationship of penicillin in the treatment of any form of syphilis has not yet been established.

It appears that the minimum dose in early syphilis should be 1,200,000 units, and probably should be higher. This amount is administered in an 8-day period. An individual dose of 20,000 units is repeated every 3 hours.

It is probable that the most effective treatment of early syphilis may prove to be a combination of penicillin and mapharsen.

Nothing can yet be said about the dosage in late syphilis.

Since therapeutic shock (Herxheimer reaction) occurs, this danger must be guarded against in some forms of late syphilis by the use of smaller preliminary dosage, as in the use of other highly spirochilidic drugs.

It is possible that smaller doses for longer periods may be more effective in neurosyphilis.

Large dosage must be avoided for the first 48 hours in the treatment of syphilis of pregnancy because of the tendency to produce abortion. The individual doses for about 2 days should be about 10,000 units, after which higher doses can be given.

No dosage has yet been established for the treatment of infants. Total dosages now being used vary from 16,000 to 19,000 units per pound of body weight. This is divided and given every 4 hours for 8 days.

**Penicillin Prophylaxis in Syphilis**

Since syphilis and gonorrhea can occur as dual infections, and since the incubation period of gonorrhea is shorter than that of syphilis, the use of penicillin in the treatment of gonorrhea may introduce confusion in the management of cases in which the two infections co-exist. This is so because the dosage of 100,000 to 150,000 units of penicillin administered in the treatment of gonorrhea does not prevent the development of syphilis, though it does seem to lengthen its incubation period to 52 days or longer.

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Penicillin has an immediate and profound effect in early syphilis. The organism rapidly disappears from the lesions, the lesions heal quickly, and there is a trend toward serologic reversal. Since, in addition to these effects, there is a tendency for the infection to relapse, further study is needed to determine the best plan of treatment.
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Herxheimer reactions occur but are not serious in early syphilis.

If penicillin is used alone, very large dosage is necessary. At the present time some of the best results have been obtained by combining a small dosage of penicillin with a subcurative dosage of mapharsen. This indicates synergism of the two drugs.

**Penicillin Therapy in Syphilis and in Congenital Syphilis**

The number of cases treated in this category is very scant, but the following observations can be made:

1. The drug has the ability to cure or to suppress syphilis in pregnancy. Miscarriage, stillbirth, and neonatal death has been prevented, and the infants have been healthy.

2. The larger doses of penicillin produced threatened abortion during the first 48 hours. When the drug was discontinued the symptoms subsided, and did not recur when it was resumed 24 hours later. Because of this tendency it is advised that ½ the usual dose be used during the first 48 hours.

Grossly infected infants can be harmed by the injudicious use of penicillin, as with other antisyphilitic drugs. The treatment should be used with extreme caution. The dosage should be reduced, and proper general pediatric care should be emphasized.

**Penicillin Therapy in Late Syphilis**

The Penicillin Panel of the National Research Council is studying the effect of penicillin therapy in various types of late syphilis. Some few preliminary remarks can be made after scanning the literature.

Gummatous lesions of the skin and bones will heal rapidly with a dosage of 300,000 units.

Psoriasiform cutaneous syphilis which had failed to respond to arsenical and bismuth therapy was cured.

In neurosyphilis various degrees of symptomatic response have been obtained in paresis, tabes dorsalis, meningo-vascular neurosyphilis, and primary optic atrophy.

Some effectiveness is indicated in interstitial keratitis, optic neuritis, and iritis.

Smaller doses seem to have a good effect, particularly in neurosyphilis. The effect probably being due to a stimulation of the patient's natural defensive mechanisms.

Herxheimer effects can be serious, and must be carefully avoided.

In all types of late syphilis penicillin had a tendency to reduce the reagin titre in the blood. This effect was observed in 50 per cent to 60 per cent of cases. Only 5 seroresistant cases have been treated. One became negative.

In neurosyphilis the abnormal spinal fluid improved in varying degrees but not in any spectacular fashion in the short period of observation.
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Conclusions

In conclusion it seems safe to observe that the treatment of early syphilis is about to undergo a revolutionary change. The therapeutic action of penicillin parallels that of the arsphenamines, and is remarkably free from injurious effects. Late syphilis will continue to be a problem since many of its pathologies are irreversible, but it seems that this new drug will eventually take an important place in its management.

References

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Edwin H. Cressman


INFARCTION OF THE PLACENTA

Julian Lansing Mines, III
Resident Obstetrician
Osteopathic Hospital of Philadelphia

The lowly "afterbirth" that down through the ages has been buried and destroyed, may contain within itself many secrets. The purpose of this paper is to direct more attention to an important organ, an organ with a short but vital life.

During recent years, the diagnosis of placenta praevia by roentgenography has become more dependable, due to the utilization of the Snow and Powell technique, and variations of it. These procedures enable one to visualize the soft tissues of advanced pregnancy. It has been observed by radiologists that many films made during this period have shown areas of altered density at the placental site. This has given rise to the assumption that these areas might indicate the presence of infarcts. It was this observation and this assumption which prompted this study of the production and effects of placental infarcts. Their presence, and possible effects, have been the subjects of much discussion, but few, if any, conclusions have been reached.

Apparently the small, white infarcts which appear to some extent in practically all placentas, are merely the result of a senile degeneration of an organ which at term has performed very important functions, but whose life cycle is at an end. These infarcts are small, fibrotic or calcareous deposits which feel sandy on palpation. They are distributed generally throughout the placental tissue, with a preponderance on the maternal surface. Microscopically, they may appear as circumscribed areas which have undergone complete necrosis, or the entire mass may have been changed into fibrin. Sometimes there are evidences of obliterating endarteritis and periarteritis. Certainly we must look upon this type of infarct as being within the limits of normality.

The type of infarct which concerns us most is the large red, or young infarct. These are rather pyramidal in shape, extending deeply into the placental substance. When present, it is not uncommon to find them involving an entire cotyledon, or group of cotyledons. In fact, they may be so extensive as to interfere greatly with foetal nutrition, causing the death of the foetus. In patients suffering a severe nephritis, stillbirths probably result from this mechanism, because it is this type of patient who often exhibits such infarctions. It would appear that daily injections of glucose, as well as of progestin and estrogens, might save some of these babies carried by mothers suffering from nephritic conditions. This treatment seems logical because it is known that glucose can be transmitted through the placental mechanism to assist in foetal nutrition. It also may be as-
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sumed that a failing placental organ will be a poor producer of progestin and estrogen, two substances necessary to normal gestation. The manner in which these large, red infarcts are produced has been a much debated subject, but by piecing together known facts, the following mode of production may be postulated.

Blood fibrinogen levels during pregnancy are increased, ranging from 0.3 - 0.7 gm. per cent. An even greater increase is noted in eclampsia where the range may be between 0.36 and 0.95 gm. per cent. As the blood fibrinogen level rises, the clotting time decreases, facilitating fibrin formation in the intervillous spaces where the circulation is sluggish. This suggests a possible reason for the presence of large, red infarcts in the placentas of eclamptic and pre-eclamptic mothers.

Thus far, the only result of infarction as described, has been an occasional stillbirth when the chorionic destruction has been extensive. But there are many other physiochemical changes occurring in the maternal organism, and perhaps in the foetus as well, which should be given further consideration. When there is tissue destruction, with autolysis present, certain split protein compounds are liberated which may affect greatly the course of pregnancy and the puerperium. As the chorionic villi are being destroyed, histamine, guanidine, and tissue fibrinogen (thromboplastin, cephalin) are deposited in the intervillous spaces. These substances are toxic, and may cause altered physiology, both locally and generally.

Once infarction is inaugurated, a vicious cycle is probably set up, and further destruction is encouraged by the production of these substances. The increased amount of tissue fibrinogen by still further shortening the clotting time, and the histamine by increasing capillary permeability, both add to the destructive factors present.

Histamine is an amine derived from histidine, an amino acid, by removal of the carboxyl group.

\[
\begin{align*}
\text{HISTIDINE} & \rightarrow \text{HISTAMINE} \\
\text{CH} = N & \quad \text{CH} = N \\
\text{C} - \text{CH}_2 - \text{CH} & \quad \text{C} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 + \text{CO}_2 \\
\text{NH} - \text{CH} & \quad \text{NH} - \text{CH} \\
& \quad \text{NH}_2 \\
\end{align*}
\]

Histamine is a constituent of ergot, and is also known as ergomine. It is an oxytoxic substance used experimentally by many physiologists to stimulate uterine contractions. Where infarction invades the maternal surface of the placenta, the histamine liberated may tend to set up uterine contraction, as well as increase capillary permeability locally, and result in the dissection of a portion of the placenta from its uterine attachment. This theory seems plausible because placental infarctions are quite commonly associated with abruptio placenta. It is fair to assume, however, that histamine liberation would probably have no such local effect if the infarcts lie within the substance of the placenta, not adjacent to the intervillous spaces.

Guanidine, an antagonist of calcium, may possibly be derived from creatin.

\[
\begin{align*}
\text{CREATIN} & \rightarrow \text{GUANIDINE} \\
\text{NH}_2 - \text{C} - \text{N} - \text{CH}_2 - \text{COOH} & \quad \text{NH}_2 \\
\text{NH} & \quad \text{C} = \text{NH} \\
\text{CH}_3 & \quad \text{NH}_2 \\
\end{align*}
\]

Guanidine production in the area of infarction may have widespread toxic effects. Many experimenters have tried to associate it directly with the production of eclampsia. Sublethal doses of guanidine injected into dogs will produce muscular twitchings similar to the convulsions of eclampsia, as well as hepatic lesions almost identical with those found in the
sumed that a failing placental organ will be a poor producer of progestin and estrogen, two substances necessary to normal gestation. The manner in which these large, red infarcts are produced has been a much debated subject, but by piecing together known facts, the following mode of production may be postulated.

Blood fibrinogen levels during pregnancy are increased, ranging from 0.3 - 0.7 gm. per cent. An even greater increase is noted in eclampsia where the range may be between 0.36 and 0.95 gm. per cent. As the blood fibrinogen level rises, the clotting time decreases, facilitating fibrin formation in the intervillous spaces where the circulation is sluggish. This suggests a possible reason for the presence of large, red infarcts in the placentas of eclamptic and pre-eclamptic mothers.

Thus far, the only result of infarction as described, has been an occasional stillbirth when the chorionic destruction has been extensive. But there are many other physiochemical changes occurring in the maternal organism, and perhaps in the foetus as well, which should be given further consideration. When there is tissue destruction, with autolysis present, certain split protein compounds are liberated which may affect greatly the course of pregnancy and the puerperium. As the chorionic villi are being destroyed, histamine, guanidine, and tissue fibrinogen (thromboplastin, cephalin) are deposited in the intervillous spaces. These substances are toxic, and may cause altered physiology, both locally and generally.

Once infarction is inaugurated, a vicious cycle is probably set up, and further destruction is encouraged by the production of these substances. The increased amount of tissue fibrinogen by still further shortening the clotting time, and the histamine by increasing capillary permeability, both add to the destructive factors present.

Histamine is an amine derived from histidine, an amino acid, by removal of the carboxyl group.

\[
\text{CH}_2 = \text{N} \quad \text{C} - \text{CH}_3 - \text{CH} = \text{N} \quad \text{COOH} \quad \text{CH}_2 = \text{N} \quad \text{C} - \text{CH}_3 - \text{CH} = \text{N} \quad \text{NH}_2 + \text{CO}_2
\]

\[
\text{NH} - \text{CH} \quad \text{NH}_2 \quad \text{NH} - \text{CH} \quad \text{NH}_2
\]

HISTIDINE HISTAMINE

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\[
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\]

\[
\text{NH} - \text{CH}_3
\]

CREATIN GUANIDINE

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eclamptic liver. This substance also produces a rise in blood pressure, even when present in minute quantities. Blood guanidine levels are markedly increased in the eclamptic mother, ranging from 0.22 to 0.40 mgm. per cent.

Fig. 2. Multiple thrombi, so called white infarcts of the placenta. From Kaufmann’s Pathology, Vol. III, Reimann; Blakiston, 1929, p. 1728.

Fig. 3. Placenta showing multiple young red infarcts of the maternal surface. Taken from a case of abruptio placenta. White areas indicate infarction. Osteopathic Hospital of Philadelphia, 1945.

Errata
Legends under figures 2 and 3 should be reversed.

This paper has postulated a sequence of pathophysiologic events which it is thought may explain the production and effects of infarcts in the placenta. The need for greater knowledge concerning the normal and pathologic physiology of this short lived but important organ is obvious.

We wish to acknowledge the assistance rendered by Drs. Lloyd and Wheeler, of our radiology department, and by Dr. Olwen Forbes.

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Bibliography

LYMPHATIC LEUKEMIA: A CASE REPORT WITH AUTOPSY FINDINGS

WILLIAM BALDWIN, JR.
Professor of Physiology

The report of this case falls naturally into four periods of management—the first and third in the outpatient clinic, the second and fourth in the hospital. The clinical report will be presented in this order, followed by the autopsy report, and discussion of the clinical and radiologic aspects of the case.

First Clinic Period

A white male, Jewish, age 66, was first seen in the outpatient clinic on January 14, 1944. The chief complaint at the time of admission was pain in the right shoulder and inferior angle of the scapula. The pain had been present for about three years and the patient had been treated in another hospital for neuralgia and arthritis. The treatment consisted of injections, diathermy, and sedation.

History and physical examination revealed the following:

Gastrointestinal: Negative, except for intolerance to fatty foods and occasional clay colored stools.

Genitourinary: Frequency N·D = 0-2

Cardiovascular: No dyspnea on exertion.

Respiratory: Positive for postnasal drip and a history of “flu” five weeks prior to admission, for which the patient had not received medical attention.

Family history: Negative for carcinoma, diabetes, tuberculosis, insanity, cardiac disease and renal disease.

Past personal history: Positive for measles, hemorrhoidectomy in 1929, appendectomy in 1935, tonsillectomy in 1937. At the time of admission there was a positive J. B. Murphy sign, prostatic enlargement, an umbilical hernia, and a right inguinal hernia. There were no palpable lymph nodes and all other physical findings were within normal limits.

Laboratory findings:

Urinalysis: Essentially negative.

Blood count: Hemoglobin 71 per cent, erythrocytes 4,360,000, leucocytes 59,150, lymphocytes 98 per cent (57,967), monocytes 2 per cent (1183). A recheck of the white count on January 24, 1944 showed 76,700 leucocytes of which 96 per cent (73,632) were lymphocytes and 4 per cent (3068) were polymorphonuclear granulocytes.

A diagnosis was made of lymphatic leukemia, and, after consultation with the Department of Radiology, x-ray therapy was instituted April 13, 1944 and continued until April 27, 1944 as described in the latter part of this paper.

During this course of therapy there was a progressive decrease in both the erythrocyte and leucocyte count as indicated in figure 1 and table 1. During this time the patient received regular manipulative therapy for his admitting complaint, which condition improved greatly. On April 2, 1944 liver, iron, and high vitamin therapy was instituted in an attempt to combat the anemia which had appeared.

On May 5, 1944 the patient received 500 cc. of whole blood. At this time he had three groups of vesicles on an erythematous base in the left mandibular and anterior lateral cervical regions. These were thought to be herpetic lesions as there was no evidence of cutaneous leukemic infiltration. The eruptions coalesced forming one large area covering the inferior portion of the mandible and the lateral and anterior cervical regions, with extension into the clavicular area. The patient meanwhile had become very weak, and on May 5, 1944 was confined to bed with a recurring sharp rise in afternoon temperature. The liver and spleen were palpable, there was a roughening of breath sounds in both lungs, with diminished breath sounds, and dullness in the middle and lower lobes of the left lung.

First Hospital Period

The patient was hospitalized on May 27, 1944. On admission radiographic surveys of the chest and abdomen were made and the following report submitted by the radiologist.

“The chest and abdomen were examined radiographically employing survey films as requested.

“A single anteroposterior film was secured of the chest with the patient supine on a hospital litter. This film, while somewhat overexposed, shows no frank or pronounced evidence of active lung pathology. One might question the localized area of altered density in the base of the right lung just lateral to and at the level of the cupola of the diaphragm. In the base of the left lung one also notices some increased radio density about the basal bronchovascular reticulum, and it is quite likely that the changes noted on the right side are of the same nature and character. There is no massive consolidation of lung structure noted, and in the main the pulmonary fields appear negative for any change which might be interpreted on the basis of metastatic malignancy or leukemoid invasion of the lung fields. The extreme supravacuicular portion of the right apex shows diminished ventilation. This, however, might be due to pleural thickening and probably is the result of such a change, since this finding was also
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noted at examination of the chest in February of this year. The mediastinum appears to be rather prominent as to width and this might be accounted for on the basis of the patient’s position at the time of examination. The right mediastinal relief is rather straight, quite discrete, somewhat prominent. On the left side the mediastinal contour is altered by virtue of fibrosclerotic aortic arch.

“The abdominal survey film shows a rather marked disturbance in soft parts relief due to gas in the intestines and colon. The liver appears to be definitely enlarged. The spleen is not demonstrated in terms of an enlarged organ. Approximating the diaphragmatic level and extending below into the upper left quadrant of the abdomen, a rounded opacity approximating perhaps the size of a large orange, was noted. The exact identity of this soft parts shadow could not be determined. There was no displacement of the gas filled colon in the region of the spleen. The kidneys were not at all well demonstrated due to gas in the bowel and intestine. The lumbar column showed scoliosis to the left with rather marked spondylotic spurring in the bodies of the lumbar vertebrea which also appear to be somewhat narrowed on the concave side of the scoliosis.

“IMPRESSION: The bronchovascular peribronchial changes noted in the basilar portions of both lungs might be the result of lymphatic change in the peribronchial lymphatics secondary to leukemic state. They might also result from inflammatory reaction of non-specific form and be entirely independent of any variation secondary to or directly due to a blood dyscrasia.

“Mediastinal adenopathy and widening cannot be established.

“The liver appears to be definitely enlarged. Splenic enlargement cannot be established. The lumbar spine shows evidence of chronic spondylosis.”

Table 2 and figure 1 show the clinical progress and therapeutic measures taken in the management of the blood dyscrasia. Transfusions as indicated were given to control the severe anemia present on admission. An attempt was made to stimulate granulocytopoiesis by the intramuscular injection of 10 cc. of Pentnucleotides three times a day, and the administration of 4 “yellow bone marrow Glandules” by mouth 3 times a day. This therapy was discontinued at the end of one week because it was felt that there was little indication in the blood picture of even minimal therapeutic response.

Sternal puncture under sodium pentothal anesthesia was performed on June 8, 1944 and the report on the specimens submitted to the laboratory was as follows:

“MACROSCOPY: the specimen submitted was a small portion of sternum, measuring 0.7 x 0.4 x 0.4 cm. This bone was excessively dense and required a great deal of chemical action for decalcification.

“MICROSCOPY: Sections of the bone marrow submitted were not very satisfactory for examination because there was too much compact bone with little marrow. Also decalcification had to be carried out too energetically to yield good materials. These sections give the impression of increased density of the compact bone and also of the spongy bone. Considerable infiltration by fat is evident, which might well be part of the process of senility. Certain portions are highly cellular with an impression of crowding out of hemopoietic elements. We would be pleased to examine further specimens of bone.”

In consultation with the department of radiology it was decided to attempt stimulation of bone marrow function with small doses of x-ray directed to the ends of the long bones. This therapy was instituted on June 15, 1944 and continued during the patient’s stay in the hospital, and continued after his discharge to the outpatient department.

Because of the low platelet count the possibility of hemorrhagic diathesis was considered, and the stool was examined on June 1, 1944 for blood, but the test was negative. The basal metabolic rate determined on June 2, 1944 was plus 16 per cent.

In addition to the management of the blood dyscrasia, the cutaneous lesion in the region of the left mandibular, and anterior cervical regions received attention. This presented a difficult problem because of the small number of granulocytes in the blood stream. The lesion was a large confluent area of suppuration covered by a very heavy crust. Along the margins could be seen superficial, necrotic, suppurative lesions surrounded by erythema and hemorrhage. Because of the crust the bulk of the lesion could not be visualized, and hence it was impossible to determine whether sinuses existed. There was no evidence of leukemic infiltration, although the surrounding cervical lymphatics were enlarged. In spite of the absence of sensory symptoms this was thought to be a post-herpetic necrotizing pyoderma.

After consultation with the department of dermatology cultures of the lesion were made. They revealed the presence of staphylococcus aureus in a non-hemolytic flora. Smears studied revealed the presence of epithelium, pus cells, many staphylococci, and many diptheroids. Blood cultures were negative.

Treatment of the lesion consisted of warm boric acid compresses applied for one hour three times a day, and a lifting off of the crusts as they become loose. This therapy was continued from May 31, 1944 to June 6, 1944 at which time the crusts had been removed. Alkaroid powder was applied for one day, and then the lesion was washed with boric acid solution. Thereafter daily dressings of 2.5 per cent sulfathiazole
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ointment in vanishing cream base were applied after washing with boric acid. At the time of discharge the lesion had healed completely.

During his stay in the hospital the patient received soft tissue manipulation twice daily with special attention directed to the dorsal and splanchnic areas. After the temperature had stabilized he was allowed to be ambulatory. The general clinical condition gradually improved although he was suffering from edema of both lower extremities, especially the right. He was discharged to the outpatient department on July 12, 1944.

Second Clinic Period

On outpatient service the x-ray therapy was continued. Weekly blood counts were made, the results of which are shown in table 3. On July 28, 1944 palpable lymph nodes were demonstrated in the left infraclavicular region, and left axilla. On July 21, 1944 the patient complained of rectal pain and consultation with the department of proctology revealed the following findings: An external hypertrophic skin tab on the left side, and an external thrombotic hemorrhoid one-half inch in diameter on the same side. The sphincteric tone was normal. There was a general hypertrophic proctitis. The mucous membrane was characterized by easy bleeding without any break or ulceration. Because of the general physical status of the patient treatment was withheld.

Throughout the time the patient was on outpatient service the pretibial and ankle edema persisted. On August 8, 1944 a hard mass was observed on the posteromedial side of the right leg midway between the ankle and knee. This gave the patient some pain, and he received x-ray therapy directed to the mass. On August 14, 1944 the patient complained of weakness which became progressively worse in spite of transfusions of 500 cc. of whole blood on August 11 and August 25, 1944.

Second Hospital Period

He was readmitted to the hospital September 11, 1944. The blood picture changes, daily temperature, and treatment are summarized in table 4 and figure 3. At this time the erythrocytic sedimentation was as indicated in figure 4.

The general management during this period of hospitalization was along the same lines as that during his first hospitalization already discussed. The mass on the right leg presented an additional problem of management. It was treated with x-ray and on September 15, 1944 appeared to contain fluid. The skin covering the mass was thin and cyanotic, and the lesion was surrounded by a painful, indurated area. The fluid was aspirated and about 25 cc. of clear, straw colored fluid was obtained. Smears of this fluid revealed pus cells but no microorganisms. Following aspiration of lesion refilled rapidly, and on September 19, 1944 it was incised, and a small rubber drain inserted. The leg was elevated and hot boric acid compresses applied. The wound continued to drain large quantities of fluid similar to the aspirated sample. On October 6, 1944 cultures of the lesion revealed the presence of staphlococci and occasional spore bearing bacilli in a partially hemolytic flora.

On October 2, 1944 because of complaints of rectal pain proctologic consultation revealed that beneath the skin tab previously reported on the left side there was an oval punched out ulcer with undermined edges which bled easily and was very sensitive. This was treated with instillation of cabasil concentrate followed by filling with cabasil surgical powder.

The patient improved under the care outlined until October 1, 1944 after which he failed rapidly. He became bedfast on October 6, 1944, became incontinent, mentally confused, and irrational, and expired October 14, 1944.

Autopsy Protocol

Autopsy No. 44-356
Died 10-14-44; 1 P.M.
Autopsy 10-14-44; 4 P.M.

External Examination

The body was that of a small, elderly white male, said to be 66 years of age. The hair was thin, and gray-black. Parietal baldness was present. A bony elevation was seen in the left frontal area. The pupils were equal in size. Upper and lower plates were present. No petechiae were seen in the mouth.

A scar was seen in the left anterior cervical triangle. The supraclavicular glands were enlarged. The chest was barrel shaped. An incisional scar 2 cm. in length was seen over the manubrium sterni. Petechiae were noted over the right shoulder and right costal arch. Needle wounds and small hematomata were noted in the antecubital fossae. The axillary nodes were palpable.

An incisional scar was seen in the right lower quadrant. There was an indirect inguinal hernia on the right. A turbid discharge was exuding from the urethra. The inguinal nodes were palpable.

Over the outer surface of the right calf was a discolored, ulcerating area 12 x 6 cm. A central drain was in place. The right foot and ankle were edematous. The left was edematous to a lesser degree. Petechiae were evident over both tibias.

Internal Examination

The subcutaneous fat was 1 cm. thick over the abdomen. The pericardial sac contained 75 cc. of slightly cloudy straw colored fluid. The heart measured 13 x 8 x 6 cm. in situ, and weighed 270 gms. The cardiothoracic ratio was 13/22. The mitral curtain was sclerosed, and evidenced
ointment in vanishing cream base were applied after washing with boric acid. At the time of discharge the lesion had healed completely.

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Autopsy 10-14-44; 4 P.M.

External Examination

The body was that of a small, elderly white male, said to be 66 years of age. The hair was thin, and gray-black. Parietal baldness was present. A bony elevation was seen in the left frontal area. The pupils were equal in size. Upper and lower plates were present. No petechiae were seen in the mouth.

A scar was seen in the left anterior cervical triangle. The supracleavicular glands were enlarged. The chest was barrel shaped. An incisional scar 2 cm. in length was seen over the manubrium sterni.

Petechiae were noted over the right shoulder and right costal arch. Needle wounds and small hematomata were noted in the antecubital fossae. The axillary nodes were palpable.

An incisional scar was seen in the right lower quadrant. There was an indirect inguinal hernia on the right. A turbid discharge was exuding from the urethra. The inguinal nodes were palpable.

Over the outer surface of the right calf was a discolored, ulcerating area 12 x 6 cm. A central drain was in place. The right foot and ankle were edematous. The left was edematous to a lesser degree. Petechiae were evident over both tibias.

Internal Examination

The subcutaneous fat was 1 cm. thick over the abdomen. The pericardial sac contained 75 cc. of slightly cloudy straw colored fluid. The heart measured 13 x 8 x 6 cm. in situ, and weighed 270 gms. The cardiothoracic ratio was 13/22. The mitral curtain was sclerosed, and evidenced
much calcification. The apices of the papillary muscles were scarred. Other valves demonstrated no lesions. No emboli were found in the pulmonary arteries. The aorta was atherosclerotic throughout, but calcification and ulceration were not present.

Each pleural cavity contained less than 25 c.c. of fluid. The right lung was adherent at the apex and to the diaphragm posteriorly. It weighed 435 gms. A Ghon lesion was demonstrated in the upper border of the middle lobe. The lung was edematous, but the bronchi were clear. The left lung weighed 670 gms. The bronchi were filled with froth. About a third of the upper lobe was involved with an interstitial hemorrhage. The remainder was edematous.

The esophagus was not noteworthy. The rugae of the gastric mucosa were flattened, and the membrane contained petechiae. A loop of the jejunum was adherent to the oecum, and the scar in the abdominal wall. The appendix was absent. The colon presented no abnormalities.

The liver weighed 2500 gms. The surface was flecked by numerous small purplish areas. A hemangioma, 2 cm. in size was noted. Bile was expressed with ease from the gallbladder. The mucosa of the bladder was ribbed and in the lumen was a cholesterol stone 2 cm. in diameter.

The pancreas seemed slightly firmer than usual. The spleen measured 18 x 13 x 6.5 cm. and weighed 530 gms. Follicular hyperplasia was marked. The suprarenals had undergone autoysis of the medullary substance. The mesenteric and retroperitoneal nodes were enlarged and firm.

The kidneys were adherent to the perinephritic fat. They measured and weighed respectively right and left 11.5 x 6 x 4.5 cm., 10 x 5.5 x 4 cm. and 140 gms., 110 gms. Small cortical cysts were present. The capsules stripped with difficulty. The cortical surfaces were granular. The cut surfaces were pale.

The urinary bladder contained about 5 c.c. of purulent material. The mucosa was congested.

The marrow of the lumbar vertebrae appeared rather normal in the gross. That of the sternum was decidedly pale, and the ribs showed complete loss of marrow.

Gross Anatomical Diagnosis:
Nephritis—Third stage
Chronic Valvular Disease (mitral)
Myomalacia
Pulmonary Hemorrhage (interstitial)
Splenomegaly (leukemic)
Lymphadenopathy (leukemic)
Atherosclerosis
Cholelithiasis

Cause of Death:
Chronic Lymphatic Leukemia
Contributory—
Interstitial Pulmonary Hemorrhage
Myomalacia

Microscopy
Sections of the lungs demonstrate thickened interalveolar septae. The capillaries are congested. In the alveolae is seen the protein of edema fluid. Large numbers of macrophages containing blood pigment are in the alveolae. Large numbers of small round cells are seen scattered through the tissue. They are most numerous about the vessels. Many alveolae contain erythrocytes, and in some areas these are in such large numbers as almost to obscure the architecture of the lung.

Sections of the liver show the sinusoids filled with blood. Many of the hepatic cells contain blood pigment. The structures of the portal canals are almost obscured by round cell infiltration. These round cells are also noted in the sinusoids.

In one area the typical structure of a cavernous hemangioma is seen. The supporting stroma of this area is heavily infiltrated with small round cells.

Capillary congestion is seen in sections of the pancreas. In the spleen, the malpighian corpuscles are not present. The whole tissue is infiltrated by small round cells.

The lymph nodes show a loss of normal architecture with replacement by small round cells. The picture is one of monotonous uniformity.

Sections of a mesenteric lipoma demonstrate an infiltration by the same small round cells characteristic of all these sections.

In the kidney, cloudy swelling is noted. Many tubules contain casts. All vessels are congested. Here and there collections of the small round cells mentioned so often above are noted.

Sections of the bone marrow demonstrate almost complete replacement by cells of the lymphoblastic series, and fat cells. A few plasma cells are noted. The erythroblastic and myeloblastic series are almost nonexistent in these sections.

Discussion
Clinical Aspects
Although in many respects the above charts and tables present typical characteristics of lymphatic leukemia, nevertheless several interesting questions arose during the management of this case which merit discussion.
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**Microscopy**

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**Discussion**

**Clinical Aspects**

Although in many respects the above charts and tables present typical characteristics of lymphatic leukemia, nevertheless several interesting questions arose during the management of this case which merit discussion.
The occupational history of the patient is perhaps worthy of a few moments thought. He worked for years as a carpenter, hence was probably in contact with resinous woods, a fact which raises once more the question of the carcinogenic properties of these agents. The attack of so-called "flu," an acute infection, five weeks prior to the original admission, fits one of the theories proposed of exciting factors in the onset of leukemia.

Table 1 and figure 1 summarize the changes in the blood picture from the original admission until the first hospitalization. Note here the fall in the leucocyte and erythrocyte counts. Unfortunately blood counts were not obtained between January 24, 1944 and March 29, 1944, which makes full estimation of the changes during this period difficult. The leucocyte count fell rapidly from a level of 76,700 to 6,500 in a period of 12 weeks, and then gradually returned to a level (17,500) which clinically is usually compatible with a leukemic life. These changes were undoubtedly due to the irradiation therapy applied to the vegetative axis.

During this interval a severe anemia developed, the incidence of which, however, lagg'd about three weeks behind the fall in the leucocyte count. In view of the fact that blood counts were not made during the early period of irradiation therapy, the question naturally arises as to how much of the change noted was a direct result of the irradiation therapy, and how much was due to the invasion of the erythropoietic centers by lymphoblastic cells.

Table 2 and figure 2 summarize the blood and temperature picture during the first hospitalization. The sharp spiking temperature on admission is typical of an acute exacerbation of leukemia, although the leucocyte count at no time rose to the high levels seen at the time of the original admission. During this interval management of the anemia was one of the principle problems. At first this was controlled by daily transfusions and Reticulogen. Following study of the sternal puncture specimens, small doses of x-ray to the ends of the long bones were used in an attempt to stimulate the erythropoietic centers. Following the initiation of this therapy it was found possible to increase the transfusion interval gradually to once weekly, and still maintain adequate erythrocyte and hemoglobin levels. At the same time a reticulocyte response was observed. A question here presents itself. Was this change a direct result of the therapy, or merely a phase of remission in the anemic condition?

Of interest during this interval is the healing of the large pyoderma lesion in the left mandibular and anterior axillary area in spite of a marked deficiency of granulocytes. As seen in table 2, the approximate average granulocyte count was only 1200 cells per cu. mm., ranging between 0 and 4000 cells per cu. mm. of blood. The normal range is between 5000 and 7000 cells per cu. mm. We must therefore give thought to the role...
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**Table 1**

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<th>Date</th>
<th>Erythrocytes in millions</th>
<th>Hemoglobin per cent</th>
<th>Leucocytes</th>
<th>Lymphocytes</th>
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X indicates Course of x-ray therapy.
L indicates Liver, iron, and high vitamin therapy.

Of interest during this interval is the healing of the large pyodermic lesion in the left mandibular and anterior axillary area in spite of a marked deficiency of granulocytes. As seen in table 2, the approximate average granulocyte count was only 1200 cells per cu. mm., ranging between 0 and 4000 cells per cu. mm. of blood. The normal range is between 5000 and 7000 cells per cu. mm. We must therefore give thought to the role.
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<table>
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<th>Date</th>
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R indicates intramuscular injection of 2 cc. of Reticulogen.  
P indicates intramuscular injection of 10 cc. of Pentnucleotide 3 times a day, and the administration of 4 yellow bone marrow Glanules by mouth 3 times a day.  
T indicates transfusion of 300 cc. of whole blood.  
X indicates x-ray treatment.
### TABLE 2

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---

**Fig. 2—First Hospital Period.**

[Diagram showing temperature and leukocyte counts over time.]
of lymphocytes as the secondary line of defense, and in the production of antibodies. The reader might, in this connection, be interested in the experiments of Ehrich and Harris.\(^2\)

The very low platelet count during the entire course of management is interesting in view of the absence of hemorrhagic states except for the terminal interstitial pulmonary hemorrhage observed at autopsy.

The elevated basal metabolic rate of plus 16 per cent, and the rapid sedimentation (fig. 4), are characteristic findings in this disease.

### TABLE 3

<table>
<thead>
<tr>
<th>Date</th>
<th>Erythrocytes in millions</th>
<th>Hemoglobin per cent</th>
<th>Leucocytes</th>
<th>Lymphocytes</th>
<th>Granulocytes</th>
<th>Platelets</th>
<th>Reticulocytes per cent</th>
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T indicates Transfusion of 500 cc. of whole blood.
X indicates x-ray treatment.

Table 3 represents the blood changes during the second period of outpatient management. During this period the patient was ambulatory until just prior to his readmission to the hospital. The leucocyte count remained approximately constant, but the erythrocyte count declined in spite of the continuance of x-ray therapy to the long bones. The fact that the reticulo­cyte response remained relatively high suggests that perhaps there might have been some response in the erythropoietic centers.

Figure 3 and table 4 follow the blood picture and temperature during the final hospitalization. On admission, the severe anemia and spiking temperature are characteristic of an acute exacerbation of the leukemic state, followed by remission, and then another exacerbation during which the patient expired. During this stay in the hospital the problem of management of the lesion on the right leg presented itself. It apparently originated from lymphatic blockage and glandular breakdown. This opinion was based on the characteristics of the drainage, and the severe edema of the extremity distal to the lesion. When the lesion failed to respond to irradiation therapy the decision to incise and drain was made.

---

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Table 3

<table>
<thead>
<tr>
<th>Date</th>
<th>Erythrocytes in millions</th>
<th>Hemoglobin per cent</th>
<th>Leucocytes</th>
<th>Lymphocytes</th>
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T indicates Transfusion of 500 cc. of whole blood.
X indicates x-ray therapy.

in spite of recognition of the fact that the chances of healing were slight, and the danger of infection great. It was felt that further delay in establishing drainage would result in spontaneous breakdown, with even greater danger of infection. The patient was relieved of a great deal of pain following the surgical establishment of drainage.

During this phase it is of interest to note the almost complete disappearance of granulocytes, due, as was later confirmed at autopsy, to the replacement of the myeloblastic series of cells with lymphoblastic.

The points discussed above seem to the writer to be those of greatest clinical interest and should be, so far as possible, integrated with the radiologic discussion and autopsy findings.

### Table 4

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R indicates intramuscular injection of 1 cc. of Reticulogen.
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**Radiologic Aspects**

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in spite of recognition of the fact that the chances of healing were slight, and the danger of infection great. It was felt that further delay in establishing drainage would result in spontaneous breakdown, with even greater danger of infection. The patient was relieved of a great deal of pain following the surgical establishment of drainage.

During this phase it is of interest to note the almost complete disappearance of granulocytes, due, as was later confirmed at autopsy, to the replacement of the myeloblastic series of cells with lymphoblastic.

The points discussed above seem to the writer to be those of greatest clinical interest and should be, so far as possible, integrated with the radiologic discussion and autopsy findings.

TABLE 4

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<th>Date</th>
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plus 1 al., h.v.l.—.95 cu., r.p.m.—39, port size—8 x 20 and 10 x 18 cm. 
Treatment was continued until each port received in total 624 r in air. 
The treatment cycle was concluded April 19th.

The patient received no further irradiation until June 15, 1944, at 
which time at the instance of the clinician irradiation was employed for the 
purpose of exciting changes in the bone marrow from the standpoint of 
production of granulocytes. This treatment was administered under the 
high voltage tube in doses ranging from 19 r to 39 r in air directed to the 
proximal femora, sternum, proximal limits of the humeri and also to the 
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day intervals, with each portal receiving in total from 78 to 117 r. This 
series of treatments was completed September 29th.

A review of all of the factors pertinent to this case establishes clearly 
and with definiteness the necessity for full and complete cooperation be­
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It is our custom to withhold splenic and direct lymph node irradiation 
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