

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

Massive Arsenotherapy
In Syphilis

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

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during the school year, October to May, inclusive.

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William A. O'Brien, M.D.

I. LAST WEEK

Date: January 31, 1941
Place: Recreation Room
 Powell Hall
Time: 12:15 - 1:10 P.M.
Program: Movie: "That Inferior Feeling"

Syphilis of Eye
 Francis M. Walsh

Discussion
 Walter Camp
 Arild Hansen
 J. C. McKinley

Present: 152

Gertrude Gunn
 Record Librarian

- - -

II. MOVIE

Title: "The Whalers"
 A Walt Disney Short

Released by: R-K-O

- - -

III. ANNOUNCEMENTS1. BORN

Charles and Clarice Hayden, a son,
 their second, on January 30, 1941.
 Weight 7 pounds 8 ounces.
 Congratulations.

2. MARRIED

Northrop Beach, son of Professor
 Joseph Beach and grandson of President
 Cyrus Northrop, to Caroline Wiggin,
 on Sunday, February 2, 1941.
 Congratulations.

3. MID-WESTERN RADIOLOGISTS

FIFTH
 Annual Clinical Conference
 of
 MID-WESTERN RADIOLOGISTS

Friday and Saturday
 February 14, 15, 1941

at
 Rochester, Minnesota

A cordial invitation is extended
 to all those interested.

- - -

4. PEDIATRIC SEMINARS

Winter Quarter - Mondays at 12 noon.

Feb. 10 The Physiology of
 Renal Circulation -
 Dr. Harvey Hatch

Feb. 17 Biochemistry in
 Psychiatric Practice -
 Dr. Reynold Jensen

Feb. 24 Experimental Hypertension and
 the Therapeutic Action of
 Renal Extracts -
 Dr. Northrop Beach

Mar. 3 The Relationship of Chemotherapy
 to the Various Strains of
 Streptococci -
 Dr. Edward Strem

Mar. 10 Chemotherapy in Pneumonia and
 Its Influence on Blood Lipids -
 Dr. A. V. Stoesser

Mar. 17 The Physical and Mental Health
 of Children under War Conditions-
 Dr. Eric K. Clarke

- - -

IV. MASSIVE ARSENOTHERAPY IN SYPHILIS
BY THE CONTINUOUS INTRAVENOUS
DRIP METHOD.

Lawrence M. Nelson

Prior to 1909, when Ehrlich announced the synthesis and early successful experiments with salvarsan, the treatment of syphilis had, with the possible exception of mercury, been relatively non-specific; so non-specific, in fact, that Boeck, the great Norwegian syphilologist and dermatologist, gave no treatment to the patients with primary syphilis who came to his clinic in Oslo from 1891 to 1910 since he thought the natural immune reaction of the patient to be more capable of dealing with the disease than the drugs then available⁹. With the synthesis of salvarsan, Ehrlich believed he had found a specific, simple method of anti-syphilitic treatment which could be administered in one injection and that therapia magna sterilisans had at last become a reality.

Salvarsan was given intramuscularly, subcutaneously, and intravenously with almost miraculous results. Wechsleman¹⁹ reported in 1911, many cases of early, late, and congenital syphilis who had rapid symptomatic improvement subsequent to the administration of one injection of 0.3 to .55 gm. of salvarsan. In many of these patients, the Wassermann reaction became negative and remained so during an unspecified period of observation; however, this author early found that "occasionally there is faulty involution so that a second injection is required" and he stresses the fact that the question of recurrence was not yet answered. Ehrlich⁶ himself suggested the possibility of giving one injection intravenously for the immediate action of killing spirochetes wholesale and following the intravenous injection in forty-eight hours with an intramuscular injection which was to exterminate any remaining spirochetes by its prolonged action; however, experience proved these methods ineffectual, and Wechsleman²⁰ later gave repeated injections of both salvarsan and neosalvarsan. In 1913, he reported that he had given in quick succession doses of 0.6 to

0.7 gm. of salvarsan without collateral effects, and that he had given neosalvarsan in 1.5 gm. doses at two day intervals without harm. He did not limit this type of treatment to patients with early syphilis.

Pollitzer¹² of New York, in 1916, recommended a method of treatment which was in conformity with the type of anti-syphilitic treatment in vogue at the time. He applied this treatment to patients who were dark field positive, seronegative, and who had not been infected for more than three months. He excised the chancre; or, if excision was impossible, he had the patient apply calomel inunctions locally twice daily for a week. Salvarsan was given 0.1 gm. for each twenty-five pounds of body weight every day for three days. The total daily dose was 0.1 gm. less for women. He usually followed this treatment with eight weekly injections of 2.0 to 2.5 grains of mercury salicylate in olive oil. If the Wassermann reaction was positive at the end of this treatment, he sometimes repeated the salvarsan.

This type of intensive "abortive" treatment was in general use until 1917, when Keidel and Almkvist, independently of each other, proposed continuous treatment for at least one year. This treatment consisted of alternate courses of mercury and arsenicals to prevent drug fastness.

Attempts to cure syphilis by abortive treatment did not disappear with the general acceptance of Keidel's and Almkvist's works. On the Continent during the early twenties, Linser's method of mixing the neoarsphenamine solution with mercury bichloride before injection was considered particularly well adapted to the abortive treatment of early syphilis. The number of treatments varied somewhat but "abortive cure" usually consisted of six injections of .45 gm. of neoarsphenamine with .02 gm. of mercuric chloride at weekly intervals. After a four to eight weeks' rest a second series of four injections was given¹³. This method had to be discontinued because of thrombosis of the veins used for injections.

Schaus and Burmeister¹⁵ reported; in 1927, a method of intensive therapy in which they gave a large quantity (1.2 to 1.5 gm.) of neosalvarsan in divided doses in a single day and repeated this dosage each week for five or six weeks. Scholtz¹⁶ administered in divided doses over a twenty four hour period a total of 0.85 to 1.0 gm. of neocarsphenamine, apparently only once.

Tzanck¹⁸, in 1938, reported satisfactory results in the intensive treatment of one hundred patients with early syphilis. He gave 1.5 g. of neocarsphenamine each day for three consecutive days and sometimes repeated the course. His series seems, perhaps, to lack adequate control. Although he reports no fatalities in his early series, subsequently he has had two deaths³.

These forms of intensive treatment have been dropped from the armamentarium of American syphilologists. At the present time, the accepted treatment of early syphilis consists of alternating or combined continuous treatment with the heavy metals and arsenic over a period of not less than fifteen months and preferably eighteen months or two years. Such a course of treatment, while necessary for the most effective care of the disease, is a serious handicap to the patient. It necessitates weekly office or dispensary visits which may cost the patient considerable time lost from work. He often tires of the procedure, and, as the clinical signs of the disease disappear, he feels that he is well, and consequently he does not continue his medication. Seventy per cent of patients with early syphilis are lost within the first year after diagnosis, and do not receive the optimum amount of treatment. Inadequate treatment of early syphilis tends toward clinical relapse, particularly neuro- and mucocutaneous. Furthermore, with the present system of treatment of early syphilis, the patient is given one injection of an arsenical with or without an accompanying injection of bismuth; and then he is sent out to mingle with his fellow men for a varying period of time, during which time his lesions still contain the *treponema pallida* and are still capable of infecting other people.

The obvious disadvantages of the present method of handling early syphilis make some modification desirable. This modification should be at least as effective as our present methods; it should be safe; it should sterilize the lesions rapidly to minimize the spread of the disease; and it should be economical, so that the patient may take the treatment with as little time lost, and at as small a cost as possible. The method of treatment devised by Baehr, Chargin, Hyman, and Leifer may have these advantages.

This work was conceived after Hyman and Hershfeld⁷, using large volume intravenous therapy, found that the ill effects suffered by the patient receiving intravenous fluids were due more to the rate of injection than to the substance injected. They found that they could inject 6000 cc. or more of intravenous fluids daily without ill effects, if the fluid was given slowly, and that pneumococcus, tetanus, or diphtheria antibodies⁸ could be given in large amounts, even to sensitized persons, if sufficiently diluted and allowed to run in at a slow velocity. These men speculated as to whether or not the nitratoid reaction seen so commonly in patients receiving arsenicals intravenously for the treatment of syphilis might not result from a too rapid injection of the medication. If true, then much larger amounts of arsenicals might safely be given in relatively short periods of time. Acting upon this assumption, Chargin, Leifer, and Hyman² treated twenty-five patients with relatively massive doses of neocarsphenamine given over a short period of time. The patients were all males, in good health except for syphilis, and were in the primary or early secondary stage of the disease. The technique consisted of alternate injections of 100 cc. of 5% glucose in forty minutes followed by 50 cc. of 5% glucose with 0.1 gm. of neocarsphenamine in 20 minutes, repeated hourly for ten or more hours on four or five successive days. The average amount of neocarsphenamine given to each patient was 4.0 gm. (limit of 2.4 to 5.0 gm.). There were no serious reactions in the series.

Of the twenty-five patients, six were lost from observation within the first nine weeks following treatment. Of the nineteen remaining, eighteen had negative serologic tests for syphilis at the end of 16 weeks observation. The one whose reaction remained positive had received only 2.9 gm. of neoarsphenamine.

The results of this treatment were so satisfactory that it was deemed advisable to treat another and larger series of patients. Consequently, in cooperation with the New York Hospital, Bellevue Hospital, the U.S.P.H.S., and the New York City Health Department, the work was continued at Mt. Sinai Hospital³.

The second group consisted of 86 males with primary or early secondary syphilis. The treatment was given exactly as in the first group except that the total dose of neoarsphenamine averaged 4.1 gm. In this group, there were four frank failures, two of which had cutaneous relapses (one possible reinfection) and two had serologic relapse. At the time this series was reported, (Sept. 13, 1939) seven other patients had not undergone complete serologic reversal. One patient died of hemorrhagic encephalitis, the result of treatment, and seven patients disappeared from observation. The clinical and serologic results in the patients treated with neoarsphenamine may be summarized in the following table:

| | <u>1st</u> <u>Series</u> | <u>2nd</u> <u>Series</u> | <u>Total</u> |
|--|-----------------------------|-----------------------------|--------------|
| Follow-up | 5 years | 1 year | |
| Number followed | 12 | 78 | 93 |
| Sero-negative and well | 13* | 67 | 80 |
| Per cent | 86.6 | 85.9 | 86 |
| Failures: clinical or sero-relapse | 1# | 4' | |
| Doubtful sero-positive | 1 | 7* | 8 |
| Maximum per cent failure | 13.4 | 14.1 | 14.0 |

* One definite reinfection after three years

Questionable reinfection

' One serologic and two chancre redux.

The death from encephalitis and the numerous less serious complications of treatment with neoarsphenamine, notably neuritis, led Baehr and his associates to try a less toxic arsenical. Mapharsen was substituted for the neoarsphenamine. Since a mapharsen solution is stable, it can be dissolved in the solvent in relatively larger quantities. Sufficient may be dissolved in the morning for the daily treatment, thus avoiding the hourly addition of fluid required when neoarsphenamine is used. The entire daily dose (240 mg.) is dissolved in 2000-2400 cc. of 5% glucose and the solution is allowed to drip into the vein at the rate of about three cc. a minute¹⁰.

Treatment with mapharsen was begun, using doses of 400 mg. for the entire course, as the usual clinical dose of mapharsen is about one-tenth that of neo-

arsphenamine; however, as infectious relapses were encountered, and as the toxicity of the mapharsen was so slight, the dose was slowly increased until the present amount of 1200 mg. given over a five-day period was reached. 157 patients were treated with the smaller doses of mapharsen before the present dosage was used. These patients received an average of 700 mg. of mapharsen. Of these 157 patients, sixteen were lost from observation. In six patients, the results were pending. At the time of the report (April, 1940) sufficient time had not yet elapsed so that the authors could tell whether or not the serologic reaction of the blood of these patients was going to become negative. Twenty-three of the patients were classified as having had unfavorable results. Nineteen of them were acknowledged failures, having had either cutaneous relapse, serum

fastness, or the serologic reaction had become positive after having been negative. None had positive spinal fluid reaction. Eleven of these patients were given a second course of massive chemotherapy, Routine antisyphilitic treatment was started on eight. The other four patients had serologic clearing, only to develop later penile lesions, which could be either a fresh infection or a mucocutaneous relapse. These four patients were re-treated with massive chemotherapy.

To Summarize:

| | | |
|---|-----|-----|
| Number treated | 157 | |
| Lost from observation . . . | 16 | |
| Results pending | 6 | |
| Unfavorable results | 23* | |
| Serologically and clinically negative after first course | 112 | 80% |
| Serologically and clinically first and second course | 118 | 84% |

*Four possible reinfections
Eleven retreated with
intensive therapy
Eight treated by conventional
therapy

No results have been published as yet on the outcome of treatment with 1200 mg. of mapharsen over a five day period, although a total of over eight hundred patients has been treated, to date. The New York group has treated and has been able to follow, for a period of up to a year and a half, ninety-eight such patients. Eighty-one (83%) of these patients achieved clinical and serologic "cure" during this period of observation following one course of treatment. Further information on a large series of patients should be available in the next few months.

Twenty-four of those patients who had an unsatisfactory result from the first course of treatment, or who became re-infected, have been re-treated by intensive therapy. Of these twenty-four patients, fifteen had a satisfactory outcome; the result is pending in six; two had an unsatisfactory result; and one has been lost from observation. One patient has been treated a third time by

this method.

Sobotha²⁰ and his co-workers estimated the arsenic excretion in the urine and feces and the arsenic concentration in the blood during the intensive treatment. With neoarsphenamine, they found an average of 21% of the administered arsenic was excreted in the urine and 50% in the combined excreta during the five days of treatment with four gm. of neoarsphenamine. The administration of mapharsen in total dosage of one gram or less over a five day period resulted in the excretion of about 67% of the arsenic. With larger amounts of mapharsen, the total percentage excreted approached that of neoarsphenamine.

The reports on the concentration of the arsenic in the blood showed that on the third day and thereafter, until the completion of treatment, the blood arsenic fluctuated between sixteen and forty micrograms per hundred cc. of blood. It is assumed that Sobotha worked with the blood of patients who received 4.0 gm. of neoarsphenamine over a five day period.

The toxic manifestations and the incidence of each are shown in the accompanying table²¹:

| | <u>Neocarsphenamine</u> | <u>Mapharsen</u> |
|--|-------------------------|------------------|
| <u>Total treatment courses</u> | 111 | 283 |
| 1. Primary fevers | 69(62%) | 115(41%) |
| 2. Secondary fevers | 71(64%) | 35(12%) |
| 3. Toxicodermas | 50(45%) | 32(11%) |
| 4. Dermatitis exfoliativa | 1*(0.9%) | 0 |
| 5. Blood dyscrasias | 0 | 0 |
| 6. Renal damage | 0 | 0 |
| 7. Jaundice | 4(3.6%) | 2(0.7%) |
| 8. Peripheral neuritis | 39(35%) | 5(mild)(1.7%) |
| 9. Cerebral symptoms (total) | 2(1.8%) | 3(1.06%) |
| a. Hemorrhagic encephalitis | 1(0.9%) | 1(0.35%) |
| b. Single convulsion | 1(0.9%) | 1(0.35%) |
| c. Disorientation | 0 | 1(0.35%) |
| 10. Fatality | 1(0.9%) | 0 |

*Received sulfanilamide for complicating gonorrhoea.

There was one death due to hemorrhagic encephalitis among the 111 patients treated with neocarsphenamine. One other case developed encephalitis but recovered⁴. There were no other serious complications, but there were enough minor toxic effects to cause the originators of the treatment to change the drug to mapharsen. Since the above table was compiled, there have been three deaths in the mapharsen series, which now numbers over eight hundred cases. Two of these (one verified at autopsy) were due to encephalitis. The third patient who died was a 40 year old hypertensive, alcoholic female. It was the impression of Dr. Tatum and of the pathology staff at the University of Wisconsin that this patient died of cardiac damage not primarily due to the mapharsen, although there were no definite findings at autopsy.

Dr. Sullivan and I attended, on January 23, 1941, the most recent of a series of meetings called by the United States Public Health Service, for a study and evaluation of the continuous intravenous drip method of treating early syphilis. It is from this meeting that the latest results appearing in this paper were obtained. Since the results were given during discussion rather than in printed prepared form, they may differ slightly from those which will be published in the near future.

It was the consensus of opinion of the men attending the meeting, that the method of therapy should be given continued trial in spite of the three deaths which have been reported to date. Dr. Tatum, of Wisconsin, was articulate in his opposition to the method, as he felt that it violated the "trinity" of host, parasite, and drug, and entirely disregarded the immune reaction of the host. Dr. Cole of Cleveland and Dr. Shaffer of Detroit have not used the method as recommended by Chargin et al, but have modified the method giving somewhat less than half the recommended dose.

It is extremely difficult to compare the results of the massive chemotherapy with that of the conventional method of treating syphilis. The Cooperative Clinical Group found that arsphenamine alone, before the administration of a heavy metal, secured the reversal of the blood Wasserman to negative by the end of the first year in 91.2 per cent of cases if the drug was given by the continuous method. The so-called "intensive treatment" (very short arsphenamine courses) which had been used previous to the massive intravenous drip method gave very poor results and predisposed to progression, relapse, and unsatisfactory treatment outcome¹⁷. Padget¹¹ reported that continuous treatment of early syphilis during the first six months resulted in 83.4 per cent clinical and serologic "cure" after long time observa-

tion. Moore, in discussing Padget's paper, states that "with the best available conventional methods of treatment, 90% of patients achieve long term "cure" by both clinical and serologic standards, and the amazingly high total of 95 per cent are clinically "cured."

There is no group of patients yet treated by the massive dose intravenous method to compare with Padget's figures either as to number followed or period of observation. Sixteen patients treated with neoarsphenamine have been followed five years or longer with clinical and serologic "cure" in 86.6 per cent. A second series followed one year showed "cure" in 85.9 per cent of cases. With a single intensive course of mapharsen, the percentages are somewhat lower (78-83 per cent) after a short period of observation. Thus, the results of the new method seem to be somewhat inferior to the best results obtainable by conventional methods.

Through the efforts of the Minnesota State Board of Health, funds have been made available for the intensive treatment, at the University Hospitals, of patients with early syphilis. To date, treatment has been completed on 12 patients under this arrangement. Seven patients were males and five were females. Ages of the patients ranged from seventeen to forty-three years. One patient was a sero-negative primary syphilitic, three had sero-positive primary syphilis, six had secondary syphilis, one had early latent syphilis, and one had an infectious relapse. Six were single, two were widowed, two divorced, one married, and one separated. The spinal fluid was normal on all except the patient with an infectious relapse, who showed a paretic colloidal gold curve, increased cells and positive serologic reaction. Repetition of the spinal fluid examination on this patient one month after the completion of treatment showed a normal fluid except for a first zone rise to two. There was no increase in the icterus index; in two cases it decreased. No constant change was found in the blood urea nitrogen during treatment. Three patients showed urobilin at some time during treatment; erythrocytes and leucocytes were occasionally found in the urine during treatment. All patients developed pain of a

varying degree in one arm or the other. This pain usually appeared the first night, was not severe, and seldom lasted more than twenty-four hours. Five patients became nauseated the first night and had no further trouble; one was nauseated during the first four days of treatment.

One patient became nauseated and chilly the last day of treatment, and one experienced only nausea. Five patients developed some primary fever the first day of injection. Secondary fever within the two days following the completion of treatment was seen in two patients.

Bilirubin was not appreciably increased during treatment. Arsenic determinations were done on four cases by Dr. Olaf Michelson. In all cases, the level on the first morning after the completion of treatment was .025 mg. per hundred cc. of blood. The arsenic level on the morning of the fourth day of treatment varied from .008 to .025 mg. per 100 cc. of blood.

The longest follow-up has been two months, and that on only one patient.

The patient who had a sero-negative primary developed a four plus Kahn reaction at two weeks, and was negative at four weeks when last checked. One patient died of hemorrhagic encephalitis, four days after completion of treatment.

Summary

1. Earlier methods of attempting intensive "abortive" treatment of syphilis are reviewed. These methods have been replaced by continuous alternating courses of an arsphenamine with a heavy metal for a one to three year period.
2. The preliminary work of Chargin, Hyman, and Leifer is described.
3. The present status of the intensive intravenous drip method of treating early syphilis and the results to date are reported.

4. The cases treated at the University of Minnesota Hospitals are briefly reviewed. No attempt is made to draw conclusions from this series as the number is too small and the period of observation too short.

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V. GOSSIP

Vincent John Hawkins was born in 1855 and died December 11, 1940. He had been a practitioner of medicine in Minnesota for the past 56 years, coming here three years after his graduation from Rush Medical College. When general staff meetings at the University of Minnesota Hospitals were started, Dr. Hawkins became an interested observer. His regular appearance at the left front table and the conscientious way he followed each program was a stimulating experience. His attendance this year was fairly regular, considering his advanced years and his failing health. Many patients looked to him not only for scientific direction but also for kindly advice. He was highly respected by all who knew him. His long and honorable career in medicine was one which we should all envy by emulation...."The Eustis Big Little News" has appeared. This is a publication by the children who are patients in the Eustis Hospital for Children, a member of the University of Minnesota Hospitals group. The publication started in a small way. The busy reporters finally picked up sufficient material for a fine first issue. Through the assistance of friends of the institution, it has been printed and circulated throughout the children's section. In a contest for the name, Bernard Bodanovitz won the prize. The presentation of the award was made by Child Psychiatrist A. H. Jensen, and much credit for the success of the publication is due to Miss Dorothy Jones, Mrs. D. D. Shaffer Lyon, and Miss Cornelia Hanson, teacher on the unit. I liked the story about the colt who broke out of his stall while the family were at church. When they came home, they found him with the window around his neck and his face in the cream bowl. There are gossip items about nurses and the patients. The paper will appear at such times as the material warrants....The enrolment in the course in Uterine Bleeding is much larger than was anticipated, as fifty are in attendance. The obstetricians and gynecologists are in the majority although a goodly number of pathologists are also here. The presence of famed gynecologic pathologist Robert Meyer on our faculty is giving American physicians in this region an un-

usual opportunity to study in this field under the acknowledged international master of the subject....A similar specialist course of three days will be offered March 3, 4, and 5, 1941 for those who limit their practice to internal medicine. It will be on the anemias. The staff will be headed by Dr. W. B. Castle of Harvard. From the Mayo Foundation we will have Drs. Snell, Woltman, Heck, Watkins, Sanford, Higgins, and Pemberton; and from our own staff Mrs. Watson, Downey, Hebbel, Spink, Boehrer, Wright, Hansen, Larson, and Peterson. The subject of the Anemias will be discussed from the laboratory, experimental, and clinical viewpoints....Among others, Dr. Philip Hench of the Mayo Clinic will discuss Social Factors in Arthritis at the course for Medical Social Workers, February 13-15, and at the course for Dietitians, February 20-22, the discussion on Vitamins will be led by Edgar S. Gordon, Associate in Medicine, University of Wisconsin. The medical staff members on the Dietetic faculty will include Drs. Kernan, Spink, Dippel, Shapiro, Stoesser, Moen, Hansen, Layne, Rae and Burr, Philip Brown of the Mayo Foundation, and E. L. Tuohy of Duluth....Plans are under way for the course for Minnesota physicians on the Care of the Newborn Infant to be given March 6, 7, and 8, and the course for Obstetric and Pediatric Nurses, March 10, 11, and 12, which happens to coincide with the dates for the regional meeting of the American College of Surgeons which will be held in Minneapolis. One of the features of this meeting will be a public health lay education program in Northrop Memorial Auditorium. There will be a formal program at the Nicollet Hotel with special programs and clinics in all the hospitals, including the University of Minnesota. There will be sections for both physicians and hospital personnel, and if past experience is any guide, this will be quite a worthwhile meeting. The American College of Surgeons conducts these meetings from time to time in various sections of this country and Canada, the last one in this region having been in Winnipeg....Roderick Heffron, Associate in Medicine, Commonwealth Fund, who was to have been a guest of the University next week, is unable to come because of illness. He is planning the trip for a later date.....