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Intensive treatment of syphilis

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I

"An introduction to intensive therapy of syphilis"

The Renaissance of interest in syphilis which occurred between 1905 and 1910 was brought about through the discovery of the causative organism by Schaudinn, the diagnostic serological test by Wassermann, and the potent anti-syphilitic drug Arsphenamine by Ehrlich. By the proper use of these three aids, the two objectives of therapy of early syphilis, control of infectiousness and radical cure can be realized. For example, the darkfield examination allows recognition of the disease, before the Wassermann test becomes positive, and permits institution of therapy during the seronegative primary stage, the period of "Golden opportunity." (21)

Ehrlich and his co-workers after diligent research, finally discovered arsphenamine in 1907, it being the 606th product investigated, it was popularly called 606. It came into wide use in syphilotherapy in 1909-1910 and treatment with this drug was based on Ehrlich's concept of "Therapia Sterilisans Magna," that is, therapeutic sterilization of the body after a few large doses of the drug. Unfortunately this was not true, at the time, for arsphenamine, and it was not appreciated until some years later, that with the technique in vogue then, many months of continuous treatment are necessary to control syphilis.

Within a year of the discovery of Salvarsan, it became evident that a single dose was not curative for syphilis. Attempts were thereupon made to bring about a rapid cure by means of a short intensive chemotherapeutic attack. As early as 1910, Hoffmann attempted modifications of this plan of treatment, but it was not tried on a large scale until 1916 when Pollitzer suggested a plan of treatment for early syphilis which required the daily administration for 3-4 days of large doses (.5-.6 gm.) of arsphenamine. Following publication of Pollitzer's results, the scheme of treatment he proposed was extensively tried by a large number of workers. It soon became evident however, that the majority of the patients treated by this method later developed infectious mucocutaneous relapse or later progression, particularly in the central nervous system.

The results of various modifications of the so-called "abortive" treatment of early syphilis was summarized in a condemnatoryfashion by Werther (1928). However, Pollitzer's method especially continued in vogue in some places until 1932 when the results of the study of the treatment of early syphilis by the Cooperative Clinic Group appeared. In the material of this study was included comparison of the results

of the Pollitzer method with conventional continuous, intermittent and irregular treatment schedules. The Pollitzer method comprises the use of .6 gm. of arsphenamine every day for 3-4 days, alternating with a more or less prolonged heavy metal series. The results following the Pollitzer method were as poor as those of haphazard or irregular treatment. (44)

Considerable harm can be done by using an improper technique to inject a few doses of arsphenamine and dismissing the patient as cured when the Wassermann reaction becomes negative, or visible lesions heal. No treatment at all, may be better than poor therapy. Poor therapy allows a higher incidence of serious late lesions, and these appear earlier than they would otherwise. Furthermore infectious relapses and serious neuro-recurrences are the price of poor treatment. The chance of the patient curing himself by his own immunological defense mechanism is decreased by 50% through inadequate medication. (21) It is unfair to the patient and to the community at large, to allow the parctice of poor treatment to exist, since through its inadequacy, many new cases will appear, through unrecognized infectiousness. Many medical crises will develop in later life due to the supposedly cured disease, and faith in treatment will be destroyed.

The suggestion, somewhat along the line of Ehrlich's original plan and along the ideas developed by Pollitzer, that very large doses of arsenicals might be given with safety in the treatment of syphilis was first made by Dr. Louis Chargin, syphilologist at Mount Sinai Hospital. Dr. Chargin first obtained the idea of treating syphilis in this way, when he read of the work of Hirschfeld, Hyman and Wagner, who observed that "speed shock" could be prevented by very slow intravenous administration (60-90) drops per minute. (25) This work had been done in 1931, and in an article by Hyman in 1935, he demonstrated that the rapid I.V. introduction of pharmacologically active or inert chemicals, drugs and biologic fluids might give rise to alarming, and at times fatal symptoms, this is the "speed shock" syndrome. It was further shown, that highly toxic substances could be administered safely by a slow continuous I.V. drip. (9) Realizing the toxicity of the arsenicals, the difficulties of Pollitzer, the progress in treatment methods, and the introduction of neo-arsphenamine, he decided to take under experiment the massive drip treatment of syphilis.

In announcing the new concept of treatment, Drs. Chargin, Hyman, Leifer and co-workers made it

known that this massive dose, short term treatment of syphilis was an attempt on their part to treat the primary and early secondary stages of the disease by means of massive doses of neo-arsphenamine and later on Mapharsen, given over a few days by continuous intravenous drip, without subsequent antisyphilitic therapy. (60)

Their treatment involved the intravenous injection of five to six times the usual maximum therapeutic dose of neo-arsphenamine or ten to fifteen times the comparable dose of Mapharsen during a period of 4-5 days. The injection continues for fifteen hours a day. The immediate clinical and serologic results obtained in a limited series of patients (394) were quite favorable. However, the incidence of untoward reactions was high, particularly peripheral neuritis, fever, hemorrhagic encephalitis and toxicodermas. The great public health and economic advantage of such therapy was evident, but considerably more controlled clinical and experimental study was necessary to determine the late clinical results to be expected, and the hazards of the toxic reactions that might make their appearance. It had not as yet been determined if some arsenical, less useful under their system of therapy might be advantageously employed in the in-

tensive treatment method with greater success.

The treatment required one full week of hospitalization.

Since the first investigative days, though only a short while ago, great strides have been made in the field. The work done on massive dosage problems has been tremendous. A history of the progress of this work is revealed by a consideration of the methods of treatment evolved and in use at the present time. These will be taken up in detail in a later chapter.

The methods in use up to the present time, are;

1) The slow continuous drip, as practiced in New York City.
2) The rapid intravenous drip, scheduled for Detroit.
3) The multiple injection technique of Thomas and Schoch.
4) Fever therapy plus multiple injections of Thomas, Simpson.
5) One day fever and Mapharsen of Jones, Carpenter, Boak, Warren and Hanson.
6) One day fever, arsenic and bismuth of Simpson.
7) Penicillin treatment as proposed by Mahoney.

All of these methods have been tried, quite extensively, with the exception of the last, and have been found to be quite successful. Naturally, the later ones have fewer failures, due to the perfection of finer techniques, which are necessary to make this method a success.

II

"The value and pharmacology of arsenicals used in intensive therapy; with a discussion of the superiority of Mapharsen and its role in the success of intensive therapy"

Historically, as we have seen in the introductory chapter, massive dose therapy has not been a recent aquisition of the profession. It was tried almost from the beginning of the arsenical treatment of syphilis. It has however been a successful method of treatment only recently. Why is this? It cannot be attributed entirely to the recent perfection of new techniques. There must be some other factor that enters into the picture and demands consideration.

Wise and Selzberger, editors of the Yearbook of Dermatology and Syphilology, have recently called attention to the possibility that the value of the newer intensive methods of treatment may depend not so much on the imporvement in the method of administration, as on the superiority of Mapharsen over the other anti-syphilitic arsenicals.(76)

Levin and Keddie (46) state that Mapharsen is less toxic than neo-arsphenamine. Only six fatalities from Mapharsen have been reported since 1935. This rate is remarkable low, considering that over 12 million ampules have been manufactured.

Death was due to kidney damage and aplastic anemia in two cases each, and to hemorrhagic encephalitis and acute agranulocytosis in one case each.

Seven patients with thrombocytopenic purpura and

two with granulocytopenia from neoarsphenamine tolerated Mapharsen without reaction. Mapharsen may occasionally cause severe damage to the hemopoetic system.

Careful observation of the use of Mapharsen by the intravenous route, showed that Mapharsen causes fewer and milder toxic reactions than neo-arsphenamine. The United States Navy statistics on reactions to neo-arsphenamine and to Mapharsen among patients of comparable age, sex and general condition of health indicate that Mapharsen is definitely less toxic. (46)

After reading the above, it is hard to believe that Magnuson (36) could report such definite toxicity for Mapharsen. Through experiments with dogs, he found definite toxic reactions. Perhaps this is where the trouble lies, since all of the previous toxicity experiments had been run on rabbits. Perhaps he is comparing his dog experiments to the results of the rabbit experiments. Another factor in his conclusions may be, that he refuses to take into consideration the high therapeutic efficiency of Mapharsen over neo-arsphenamine, and bases his conclusions on mere mass comparison.

To contrast Magnuson's experimental findings, a clinical report, (60) states that conclusive proof

of the non-toxic character of Mapharsen has been demonstrated in an uneventful series of 275 cases.

So an analysis of his article might lead one to believe that he draws erroneous conclusions, and that Mapharsen is not the toxic drug he states it is.

Mapharsen (arsenoxide) was investigated by Ehrlich and Hata, but pronounced by them to be too toxic for clinical use, the high therapeutic efficiency of the drug not being appreciated. The chemical remained of great therapeutic interest however, because it was believed to be the oxidation product through which the arsphenamines exerted their spirocheticidal action in the body.

After several years of careful laboratory and clinical research on the anti-syphilitic use of arsenoxide, cautious reports of its value began to appear, (68) and the drug was released for study to the cooperative clinical group. The available evidence indicates that this drug is one of the most promising arsenical treponemicides for syphilotherapy.

The term arsenoxide is really a generic one, but it is used in clinical literature to signify a particular chemical, meta-amino para-hydroxy phenl-arsine oxide. From the first letters in the component parts of this chemical name is derived the term

"Mapharsen." The drug is not an arsphenamine but represents a partial oxidation product of arsphenamine.

Mapharsen contains 29% of a trivalent arsenic and is marketed as the hemi-alcoholate in nitrogen filled ampules. The physical and chemical properties of arsenoxide are such that, in contrast to the arsphenamines, the drug is neither precipitated by tissue fluids, nor does it agglutinate or hemolyze red blood cells. (22)

The dose of Mapharsen is one tenth that of arsphenamine. The average initial adult dose is 40 mg. for males, and 30 mg. for females. The absolute amount of arsenic given in a course of Mapharsen is only one tenth the amount given in a course of arsphenamine. Cumulative arsenical poisoning is therefore much less likely; and since only one tenth of arsphenamine is converted to arsenoxide in the body, (55) the therapeutic dose of the two are equally effective from the standpoint of the end product. Arsenoxide has the added advantage of having no accompanying breakdown products which must be eliminated by an already overtaxed system, such as is the case with arsphenamine. Although the toxicity of Mapharsen is about six times greater than that of arsphenamine, its clinical efficiency on the basis of arsenic content is about six times as great.

Although all the evidence is not yet available, Mapharsen appears to be superior to neo-arsphenamine, and approaches arsp enamine in the ability to cause disappearance of the surface treponemes, heal surface lesions, and effect reversal of the Wassermann reaction. It is directly spirocheticidal and is not dependent on the intermediary breakdown products for its acitivity. In fact it is believed by some to be the substance by means of which the arsphenamines act as spirochet-icides and trypanocides.

Mapharsen is well tolerated in the body, gastro-intestinal upsets are fewer, and the drug is less likely to make the patient ill. The patient is thus more willing to cooperate and continue therapy. Nitritoid reactions to Mapharsen do not occur. It can often be used in full doses in patients intolerant to arsphenamines, and appears to cause a lower inci-dence of serious skin and visceral reactions. There is some evidence that excretion may be more rapid than that of the arsphenamines, (80% excreted within one week), and that Mapharsen may therefore be given twice weekly. (22)

III

"Establishing an experimental basis for the use of intensive therapy in man"

Any new method introduced into the field of medicine should be tried first experimentally to prove its worth, in so far as is possible in the laboratory. It is in the laboratory that mistakes are discovered in techniques, drugs and methods; but the laboratory can only show results under controlled conditions. In chemotherapy the optimum therapeutic result is obtained by the introduction of the specific agent in quantities that suffice to destroy noxious invaders without seriously or permanently injuring the cells of the host. Under controlled conditions this ideal is approached in experimental animals that have been infected with syphilis in the laboratory, and then promptly treated with arsphenamine.

In human syphilis the problem offers far greater difficulties; treatment is delayed, the dosage must be agumented, idiosyncrasies are encountered, there occur technical errors in administration of the drug, and untoward reactions may follow, varying from mild and transitory distrubances to fatal poisoning. (9)

Still it is necessary to conduct laboratory experiments with a proposed treatment such as this. Laboratory animals must be chosen for specific reasons in testing any new drug or procedure. In this case the animal of choice was the rabbit.

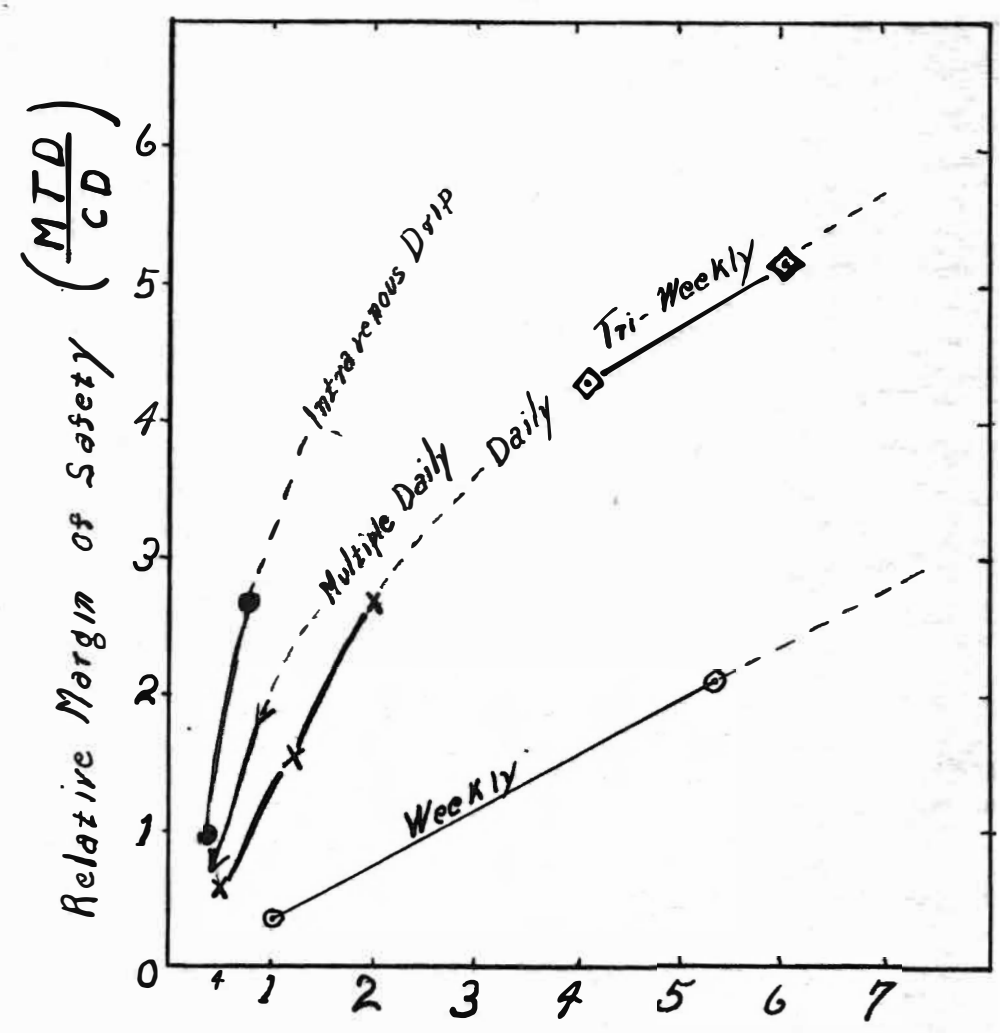
It is possible in the rabbit to study the disappearance of surface organisms, the rate of healing of lesions, and, by means of lymph node and tissue transfers to normal animals, the actual sterilization of the infection. The results should be expressed in terms of the smallest single dose (in milligrams per kilogram) capable of sterilizing the experimental animal, thus permitting, when compared with the maximum tolerated dose, an expression of the therapeutic index.

This type of study is time consuming, requiring several months for completion, costly, and not exactly translatable to human syphilis, in the sense that since syphilis in the rabbit is easier to cure than syphilis in humans the optimum dosage in the rabbit is not capable of direct translation into climical practice with equal prospect of success. But it provides information so valuable, especially as concerns the relative worth of different drugs, that it must be carried out with every new product proposed; and should be carried out from time to time for a routine testing of fresh lots of various drugs, already in acutal use, to make sure that their therapeutic potency is maintained. (44)

The problem of working out the experimental evaluation of the intensive treatment method fell to Eagle and Hogan, very able men in the field of experimental medical research. They thoroughly investigated the problem, all of its various aspects, and possible mortalities; and after extensive work, published their results in an extensive record of experiment.

The first problem they were forced to settle was one of toxicity. This involved the toxicity of drugs to be used, methods, and rates of injection. It was in working out this problem that the value of the time dose relationship was discovered. As to the animals toxicity, they concluded that, the greater the number of injections, and the longer the time period over which these injections were spread, the greater the animals tolerance to Mapharsen. (16)

The time dose relationship factors, much discussed by various authors, can best be understood by reference to the accompanying charts, which more than clearly explain the results in altering either the time factor, or the dosage of the drug. The effects of such alterations can be followed on the charts, and the reason for many authors untoward reactions can be understood on the basis of altering



DURATION OF TREATMENT (WEEKS)

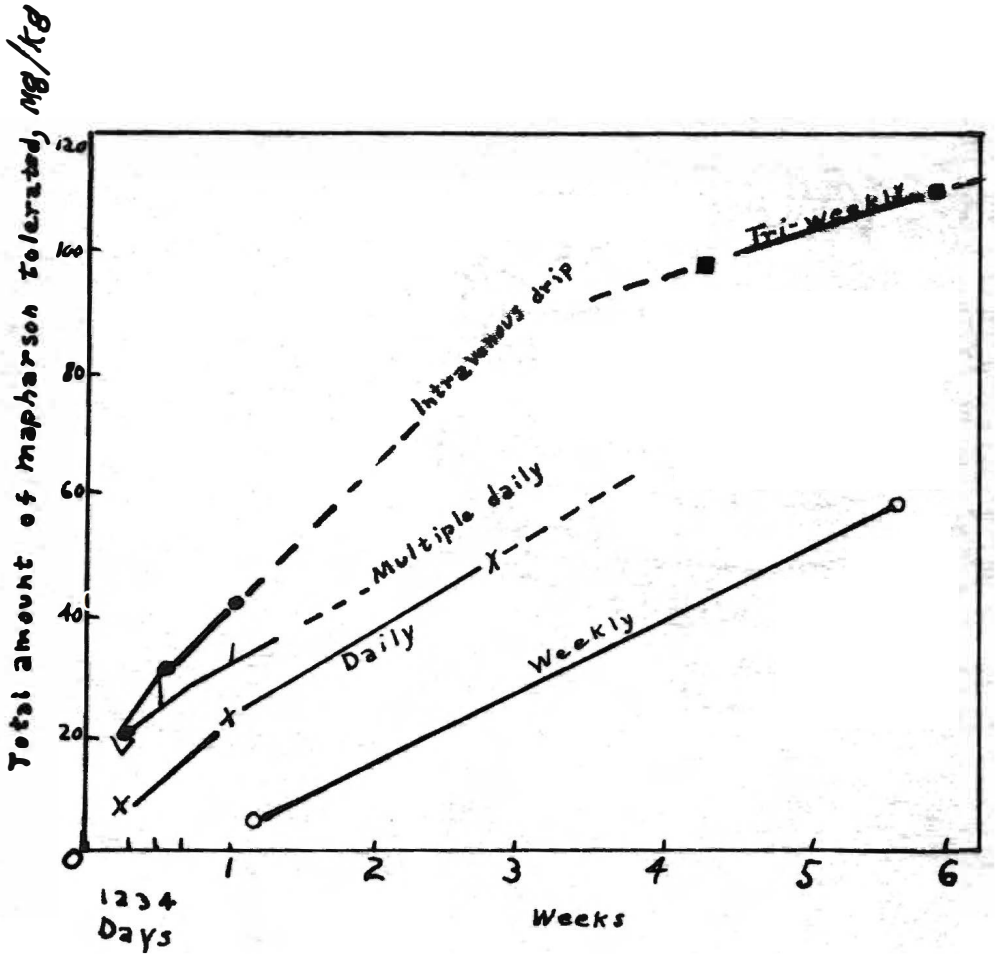
The effect of the duration of treatment and the frequency of injections on the margin of safety afforded by antisyphilitic treatment in man.

either of thses two factors.

Another of Eagle and Hogan's findings was that, the curative dose of Mapharsen in syphilitic rabbits was affected to a relatively minor degree by varing, either the total duration of treatment or the frequency of injections. Mapharsen administered by intravenous drip was usually less effective than Mapharsen administered over the same time intervals by repeated syringe injections. There was a definite suggestion also that the drug was more effective when given over a period of a few days, than it was when treatment was spread over a period of weeks, or concentrated in one day.

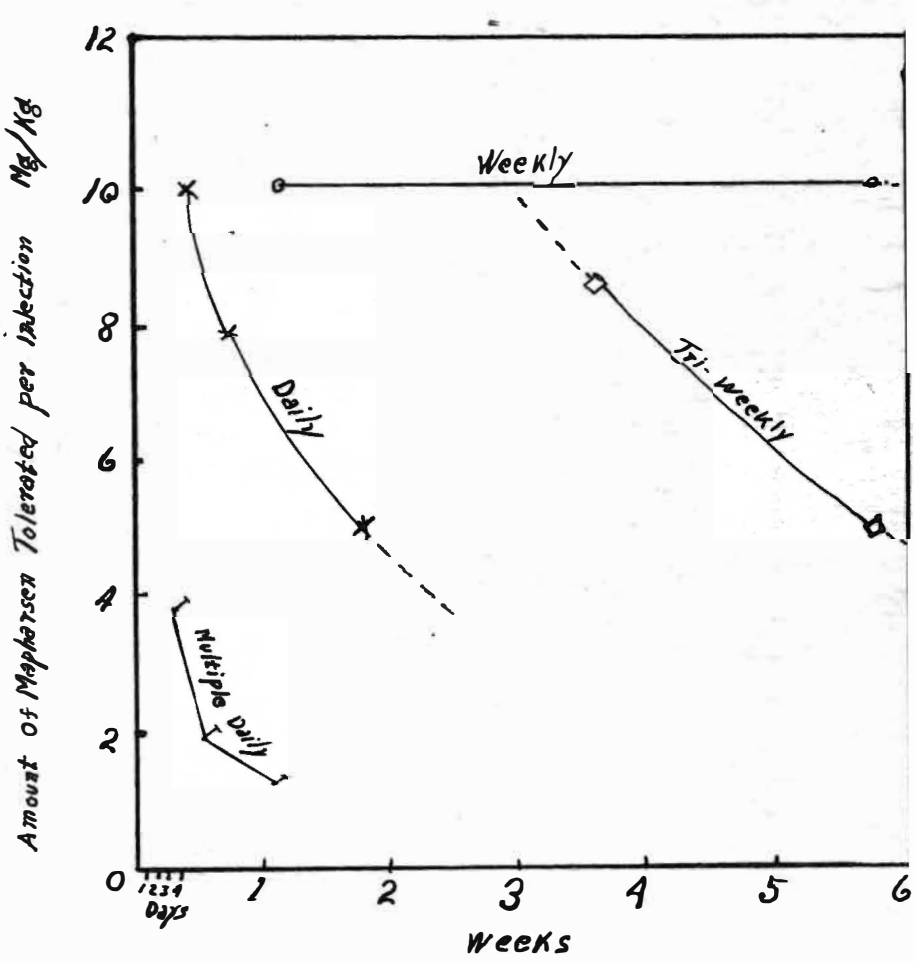
As to margin of safety, on any schedule of injections, whether weekly, tri-weekly, daily, four times daily or intravenous drip, any desired margin of safety between the tolerated dose and the therapeutic dose, can be obtained by suitable prolongation of the time period of administration.

The last finding reported by Eagle and Hogan was that in the treatment of Rabbit syphilis, treatment can be condensed with safety by increasing the frequency of injections if there is any compensatory decrease in the size of the individual treatment and an increase in their total number. (16)



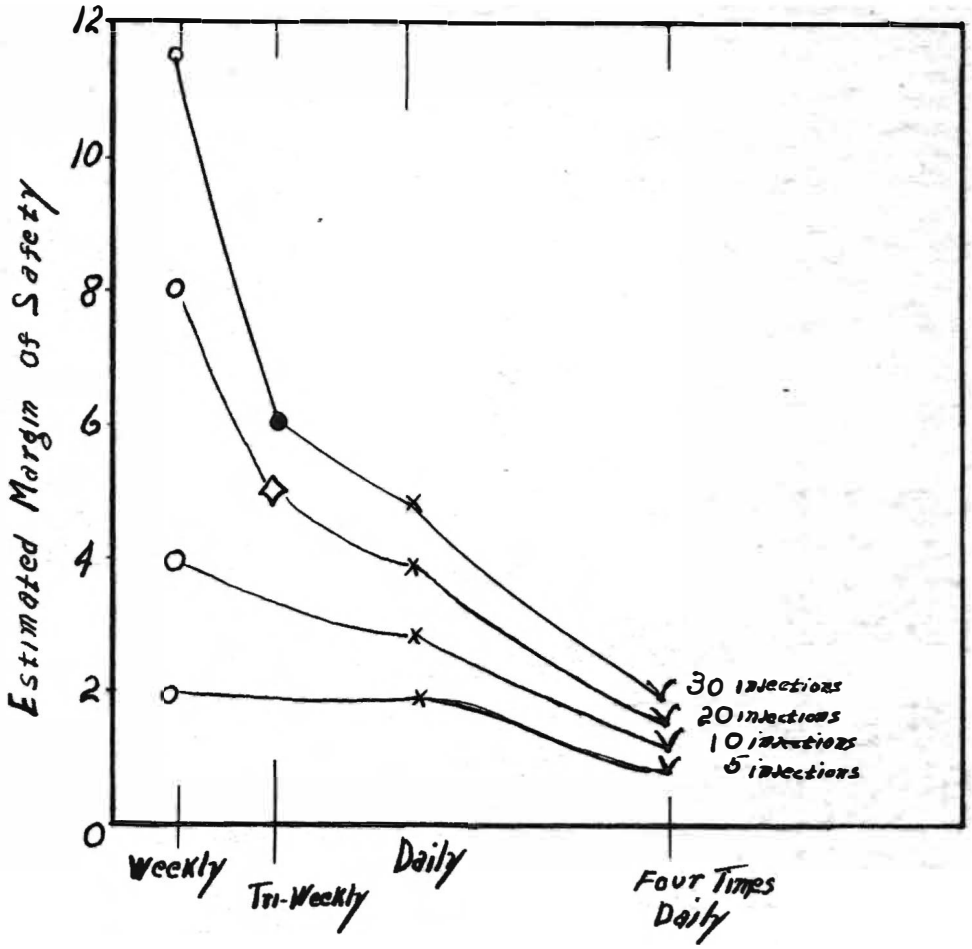
DURATION OF TREATMENT

The maximum tolerated dose of Mapharsen in rabbits in relation to the frequency and duration of treatment.



DURATION OF TREATMENT

The effect of the duration and frequency of injections in rabbits on the amount of Mapharsen tolerated per injection.



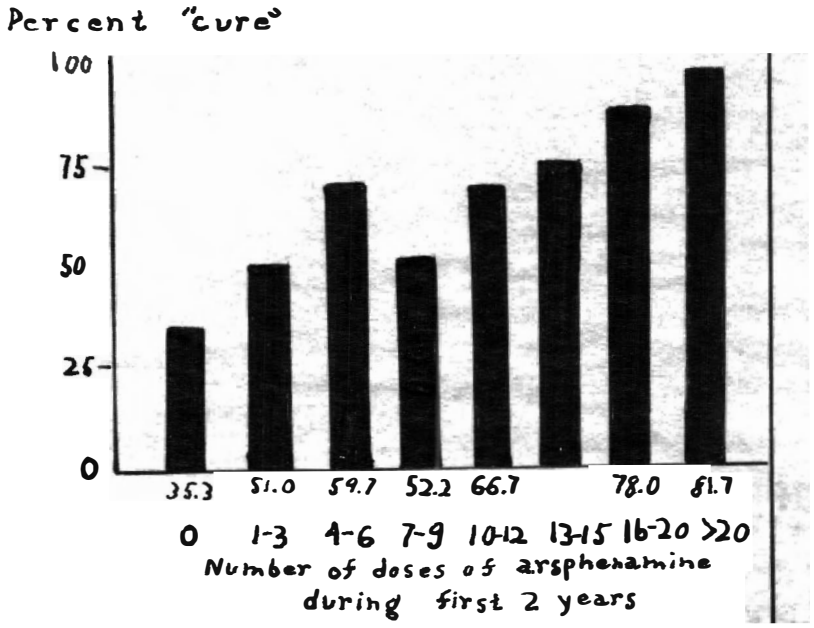
Showing that the margin of safety afforded by antisyphilitic treatment in man is decreased if injections are given at more frequent intervals, without changing either their size or total number.

(The total "curative" dose was fixed at 25mg. per kg., 1,500 mg. in men weighing 60 kg.; and the maximum tolerated dose in rabbits was used to calculate the margin of safety ($\frac{MTD}{CD}$) afforded by the various schedules. Each curve in the figure gives the estimated margin of safety for a fixed number of treatments, as affected by the frequency of injection.)

IV

"What constitutes a cure when using an intensive method of treatment; can there be an earlier recognition"

The duration of treatment in early syphilis: In 1926 Keidel made the statement that when he first adopted his plan of treatment, then in operation, he had no accurate idea how long the treatment should be continued. The evidence provided by patients who lapsed after varying amounts of treatment made it obvious that while a few were cured by one or two courses, many were not cured. Inasmuch as there is no way of differentiating the potential cure from the potential failure before treatment is begun, it seemed certain that the only safe procedure was to treat every patient up to the point necessary to cure the most resistant member of the group. As long as nine years ago, therefore, we set up as a standard one year's continuous treatment after the blood Wassermann (and spinal fluid) had become and had remained completely negative. The figures justifying this position are shown in the accompanying chart. (44) They are based on the material of the Johns Hopkins Clinic, and show quite clearly that the probability of cure rises from 35% among the untreated patients to 82% following 20m or more injections of arsphenamine in conjunction with bismuth and mercury. It is indeed unfortunate that no method exists by which the probable "cures" after small amounts of treatment can be picked out before or during



The relationship between the final outcome and the number of doses of arsphenamine administered during the first 2 years. (Padget)

treatment. This hiatus in our knowledge is responsible for the undoubted fact that some patients receive much more treatment than is actually necessary. (45)

It is estimated that 500,000 fresh cases of syphilis are reported to physicians in the United States each year. Untold numbers remain unreported, approximately 600,000 advanced cases which have never before received treatment report for the first time each year, and 5-10% of the population are infected.

The difficulty lies not in a lack of information, but in the failure both of the physician and the public to use the knowledge already available.

The concept of curability of syphilis varies with the stage of the disease.

1) Biological or Radical Cure: this signifies eradication of the last treponeme from the body, and applies only to early (primary and secondary) syphilis.

2) Symptomatic Cure: applies to late syphilis and signifies the disappearance of all signs and symptoms of the disease and the lack of infectiousness. The organisms are not killed. The serology may be positive or negative, a matter of secondary improtance. Cure in either sense, can be determined only by careful observation over a period of years. (21)

Previously it was not as important to know whether

or not the patient had biologic cure, or merely symptomatic cure of syphilis; we were treating with a standard method; we had nothing better to offer the patient; and we had a long series of time preceding, using the same type of treatment, in which to evaluate its worth. But today we may have something to offer the patient. With our new forms of massive therapy, we may be able to offer him a fast cure, never before hoped for. Whether or not this is a positive cure, we cannot say, because sufficient time has not elapsed from its introduction up to the present time, to speak properly concerning its efficacy. If is is positive, many patients that could have been treated may pass us by. The fact that this is a time of war, when it would be possible to check more closely in short time periods large groups, makes it imperative that we cease judging new treatment on the yardstick of the old.

Up to the present time we have been judging its worth by comparison to methods used in the old, long treatment method; and we have been afraid to use the new treatment, because we could not be sure of its true therapeutic effect. J. E. Moore, in an editorial, expresses a somewhat radical departure from accepted standards of evaluation when he describes a method of measuring curability by re-infection. (41)

Relapse is accepted as a clinical characteristic of syphilis. Inadequate treatment of early syphilis is accepted as one of the most potent causes of relapse. Infectuous mucocutaneous relapse or recurrent secondaries may be very extensive and typical, or localized and difficult to classify. The most troublesome is the monorecidive, or chancre redux, which may be almost impossible to differentiate from a reinfection chancre except that it occurs at the site of the previous chancre. Various attempts have been make to set up suitable criteria for differentiating reinfection from clinical relapse. Such criteria have never been entirely satisfactory, and are of special importance for differentiating reinfection from relapse in intensive treatment cases. In general the criteria for cases receiving standard treatment are hardly suitable for intensive treatment cases. So Dr. Loren Shaffer has set up a group of criteria of reinfection for intensive treatment cases.

1) Accuracy of the original diagnosis of syphilis assumed on the basis of the administration of intensive treatment by organized hospital or clinic.
2) Patient has remained seronegative, or has progressed to that state.

3) Spinal fluid examination negative prior to second infection. (This is desirable but not essential.)

4) A lesion, clinically acceptable as a chancre, develops at a site different from the first.

5) Patient is seronegative, but darkfield positive at the time of the second infection.

6) Definite exposure history for second infection. (Ideally source for second infection should be identified.)

7) If seropositive at time of supposed second infection, patient should be held in isolation without treatment until after the proper interval, at which time secondaries develop to establish validity.

8) Seropositive cases of clinically acceptable primary lesions or cases presenting characteristic secondary manifestations, with a history or remains of a chancre, may be classified as probably reinfection, if they fulfill the above criteria.

Supposed reinfections occurring within six months after intensive treatment is completed cannot be differentiated from potential super-infections. Cases occurring at a later date may be assumed to be reinfections. (61)

V

"Present acceptable methods of treatment with intensive therapy"

In the first attempts to use massive arsenotherapy, Chargin (9) treated a series of 25 patients. Neo-arsphenamine was the original drug used, and in doses of 4 to 4.5 gms. administered by a continuous intravenous drip system in a period of five days. As far as they have been able to determine some 87% of these patients have been cured. No additional patients were treated until 1937, when this method of treatment was revived. Eighty six patients with primary and secondary syphilis were treated with neo-arsphenamine by the method used previously and two year cures were reported in 91% of the cases.

When Mapharsen was first used no experience with its use in larger dosages was available. The usual recommended dose is 1/10 of the dose of neo-arsphenamine. Thus a total dose of .4 gm or 400 mg. was decided upon as the dosage amount for intravenous drip, with the technique remaining the same as that for neo-arsphenamine. Because the lower toxicity of Mapharsen was finally realized, and because the dosage employed allowed a number of failures of treatment, the dosage of Mapharsen was increased in the intravenous drip to 700 mg. and then by slow degrees through levels of 800, 1000 and finally to the recommended dosage of 1200 mg.

The rate of administration was shown to be 240 mg.

per day for five days, the 240 mg. being dissolved in 2400 cc. of a 5% glucose solution and given at the rate of 20 mg. per hour, continued over a period of twelve hours. This represents a daily dose of four times the amount usually injected (60 mg.) and a total of twenty standard doses in a period of five days. The injection is given from a gravity vacoliter at an approximate rate of 3cc. per minute.

In the accompanying chart are tabulated the results of the New York treatment series previously described using the slow continuous drip method. Series I with Mapharsen represents cases receiving less than 1,100 mg. in five days, while series II received 1,100 mg. to 1,200 mg.

The above results pretty well parallel the results now being returned from various intensive treatment centers set up about the country, using the slow continuous drip.

Various modifications of the original New York continuous drip method have been tried in different places throughout the country. In Detroit, Shaffer has developed a rapid drip modification which consists of the administration of approximately 1.2 mg. of Mapharsen per pound of body weight to a maximum dose of 180 mg. dissolved in 1,000 cc. of 5% glucose

Patients	Drug					
	Neoarsphenamine		Mapharsen I		Mapharsen II	
	Number	Percent	No.	%	No.	%
Satisfactory	87	89	109	79	82	83
Pending	4	4	5	3	9	9
Unsatisfactory	6	7	24	18	8	8
Total	97		138		99	

solution. It is given by gravity (vacoliter) requires 60 to 75 minutes for administration, and is repeated daily for five days. It requires less hospital supervision. It was hoped, even though the total dosage was decidedly less, 750 to 900 mg., than called for in the New York method; that its administration in a shorter period of time, approximately one hour, might prove equally effective.

Results of this method, as reported by investigators have closely paralleled the New York series for primary cases, but has been decidedly inferior for secondary cases. This revealing fact would seem to indicate the advisability of using larger dosages in this method, at least in the treatment of the secondary cases.

From the above there would seem to be little difference between the advisability of using the slow or rapid methods of intravenous drip therapy.

Another method of intensive treatment has been the multiple injection method. This consists of giving by syringe technique (10 cc) a dose of 60 to 100 mg. of Mapharsen once or twice daily and repeating the dosage daily until a total of 1200 mg. has been administered. This method of giving intensive therapy has been reported by Thomas (61), and Schock (52).

A dose of 60 mg. may be administered twice daily for ten days, 100 mg. twice daily for six days, or 100 mg. once daily for twelve days. Schoch has never used the latter method for ambulant clinic patients. Reports on the extensive use of this method are not complete. Thomas' report would indicate that the incidence of serious reactions is at least as high, and probably higher, than with the slow drip administration. Such methods are rather experimental, and should not be used as general therapy. (53)

As to the use of fever therapy in syphilis, Wagner Jauregg was the first to use a form of hyperthermia, malaria, for treating dementia parplytica. Later this treatment was tried in early syphilis and found to be successful. From malaria therapy we have drifted to the use of other fever producing implements, foreign protein therapy, eg. typhoid-paratyphoid intravenous injections, hot baths, the inductotherm, and the hypertherm. Their value in central nervous system syphilis is unquestioned and investigators have naturally turned to them in the treatment of early syphilis. It was an American dermatologist, J. F. Schamberg, who as long ago as 1926 reported the beneficial effects of hot baths in experimental rabbit syphilis. In 1935 Epstein and Cohen and in 1936 Neymann, Lawless and

Osborne found such treatment to be ineffective in human syphilis. This has been confirmed by Boake, Carpenter, Jones, Kampmeier, McCann, Warren and Williams, and by Simpson, Rose and Kendall. However when this fever therapy is combined with chemotherapy it seems to be a different story.

A study of 141 patients with Mapharsen and fever in 1941 indicated that very encouraging results were obtainable by using fever with .54 to .6 gm. of Mapharsen and no toxic reaction was observed. (64)

In a series of investigations conducted primarily as a study of quantitative serologic studies in early syphilis, Simpson, Kendall and Rose, after quite extensive studies using first artificial fever alone, which they found to be ineffective for early syphilis, and then instituting a treatment of combined fever and arsenicals, but conducted over a period of weeks in courses of three hour sessions, twelve in number; finally attempted a single prolonged fever treatment accompanied by chemotherapy. They reached the conclusion by means of the following; repeated determinations of the serologic titer by means of the Kahn quantitative procedure, have shown that the progressive decline in titer to negativity is essentially the same as that noted in individuals receiving a

larger total amount of both artificial fever and chemotherapy over a longer period of time. (58)

If the above is true, the single fever treatment combined with the chemotherapeutic attack would seem to be the proper angle of attack.

Because of the failure of induced fever alone (6) to cure primary syphilis in man, attempts have been made to combine fever with subcurative doses of arsenicals.

Jones (32) selected for study, patients with clinical evidence of syphilis in its early stages, who had received no previous anti-syphilitic treatment. The diagnosis was verified by darkfield and serologic examination. He set up as contradictory to this type of treatment, active pulmonary tuberculosis, heart disease class II and class III, active renal disease, perivascular disease of any type, and extreme obesity.

His treatment consisted of the concurrent use of fever and Mapharsen. The amount of the drug, and the time of administration in relation to the fever are based on results obtained in the treatment of experimental rabbit syphilis. Because animal experimentation has shown, that fever increases the toxicity of Mapharsen, subcurative amounts of the drug were

employed for the treatment of the first series of patients to avoid toxic reactions.

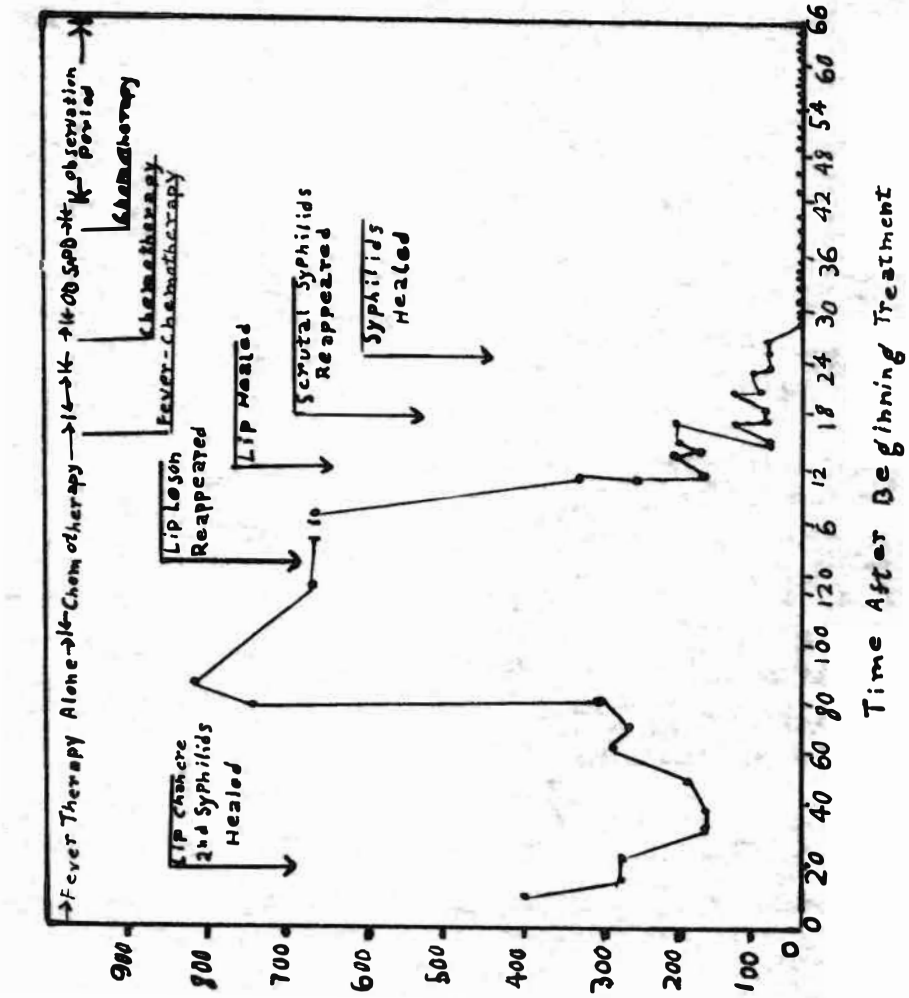
Three schedules of treatment were used which, for the purpose of clarity, we shall summarize:

a) Mapharsen: 1mg. per kg. body wt. administered during the induction of the fever, but before the temperature reaches 39.5 degrees C. The drug is dissolved in distilled water and injected intravenously.

b) Mapharsen in the amount of 1mg. per kg. body weight injected in the evening, and fever therapy is carried out the following day. A second intravenous injection of 1.5 mg. Mapharsen per kg. body weight is given at the termination of the fever.

c) Mapharsen in the amount of 2 mg. per kg. of body weight administered at the termination of the fever. The drug is dissolved in distilled water as in other schedules, then it is added to 250 ml. of a 5% glucose in a .85% solution of Na Cl and injected intravenously by the drip method. The procedure requires about fifteen minutes and is usually completed by the time the temperature has receded to 40.5 degrees C.

On the day of the fever treatment the patient is placed in a fever cabinet early in the morning. He is carefully checked throughout the course of treatment, for pulse, respiration and by means of the blood plasma, for his fluid balance. To make up the fluid depletion



Effect of artificial fever therapy alone on the clinical and werologic course of a seropositive case of primary syphilis.

intravenous solutions are administered. After five hours of fever, the patient is returned to his room. He is required to rest in bed for several hours. A few of the patients leave the evening of the treatment, but the majority rest the night in bed, and leave on the morning following the treatment.

Patients are to be followed for a period of five years, returning to the clinic weekly, during the first eight weeks, monthly for the following six months and every three months during the next year, and annually thereafter. At each follow up visit observations are made for the clinical evidence of syphilis and blood is taken for serology. At the time of initial treatment, spinal fluid is collected, or on the first visit thereafter, for examination.

As far as they have been able to follow the patients, the schedule of treatment listed under c, above, has given the smallest percentage of relapses. (58)

One of the most interesting proposals has also been announced by Simpson, and calls for only one day of treatment. The method consists in the intramuscular injection of 4 gr. of Bismuth subsalicylate twenty four hours before artificial fever therapy is begun. The patient is then placed in a fever cabinet and given continuous therapy for ten hours with

temperatures from 105 degrees to 106 degrees Fa. He is also given 120 mg. of Mapharsen in divided dosage by the syringe technique during the height of his febrile reaction. Simpson aims at reducing the time of administration of treatment from five days to one day by the combined use of fever, arsenic and Bismuth.

Further reports on this method of treatment are awaited with interest. (54-55-56)

As this is written, there is already some publicity regarding the use of the new substance penicillin in the treatment of syphilis. Absolutely nothing can be said with assurance about the usefulness of penicillin in syphilis therapy except that the subject is being investigated. The drug has been tried in a very few cases with immediate results. No one has revealed what the more important lasting effects will be. As a matter of fact there is not at present enough penicillin available to make possible an adequate trial.

Results of the use of penicillin by the armed forces in the treatment of syphilis are unobtainable. We can however gain some idea of its usefulness by reference to a study by Mahoney and Harris. (38)

A study of the usefulness of the drug was undertaken after limited animal experimentation proved that penicillin had some spirocheticidal activity.

Because of the general non toxic character of the drug, a pilot study in four humans was run, after a short experiment of its effectiveness in rabbit syphilis had been determined. The feeling was that observations could be made of the effectiveness of the drug without placing the patient in jeopardy because ultimate recovery of the patient could be assured by conventional therapy, should penicillin prove ineffective.

The animal investigation showed one important point, and that is that the time dose relationship will prove to be as important in this therapy as in the use of other chemotherapeutic agents.

Four males were investigated. Various serological tests showed them to be four plus. Each displayed a single penile ulcer, which on darkfield showed spirochetes. The duration of the ulcers were eight days, no other therapy was employed except penicillin.

The treatment consisted in intramuscular injections of 25,000 units at four hour intervals, night and day, for eight days. The total number of injections was forty eight and the total amount of the drug used was 1,200,000 units. The gluteal muscle was the site of injection. Darkfield examinations were done every four hours, and after sixteen hours no more spirochetes

could be seen.

Blood studies done daily, showed therapy was responsible for a more or less rapid and complete disappearance from the blood stream of the reacting substance measured by serologic tests.

VI

"Mortality studies in the intensive treatment methods"

Author	Number of Pts and remarks	Preparation and Dosage used	Results and Conclusions
Trautman, J. Hosp. News U.S.P.H.S. 8: 12-20 Nov. 15, 1941 (72)	62 cases of early syphilis, intended to follow procedure of Hyman + coworkers by 5 day IV drip Trt.	1) 5 cases; 240 mg. Mapharsen Over a 5 day period. 2) 43 cases, 240 mg. Mapharsen over a 12 day period 3) 14 cases, 240 mg. Mapharsen over a 28 day period. Total - 1.2 gm.	40% had headache - 1 death from hemorrhagic Encephalitis. 39% had headache, fever, nausea + vomiting Trt. discontinued in 4 cases by reaction 21% had headache, fever + toxicoderma Trt discontinued in 2 cases by reaction Conclusion: Alter Hyman method of Trt.
Sadusk, Craige, Brookens, Coole & Strauss. Yale J. Biol. + Med. New Haven. 14: 333-355 March, 1942 (59)	33 pts good physical condition. All had early Syphilis. 15 ♂ 18 ♂ 19 White + 14 Negro All pts. completed Trt.	.24gm. of Mapharsen daily for 5 days. Total 1.2 gm.	Primary + Secondary Sever; toxicoderma, Jaundice, peripheral neuritis, nausea + vomiting, thrombo phlebitis, Leukopenia, Secondary anemia, Darkfields all neg. in 24 hrs. 19 pts. completely sero-Neg. 1 pt. Trt. failure 13 pts. show weak serology at 6 mo.
Usher, B. + Hill, A.E. M.A.J. Montreal 46: 342-345	36 pts primary + Early Secondary Syph. in Excellent health.	Continuous drip: 1200 mg. total dosage of Mapharsen.	nausea/vomiting; pain in arm, Fever on 5th day Toxic erythemas in 5 pts; peripheral neuritis in 3 pts purpura in 1 pt; Spinal fluid exam. on the 6th day in 35 cases showed 3 abnormalities. A weak Wasserman; + globulin + change in colloidal gold curve. No Mapharsen Reactions. No Nitritoid crisis. No blood dyscrasias. 3 months after trt. 4 complete reversal of Serology, + 2 partial reversal.

Kaplan, B. Arch. Derm. & Syph. 45: 941-949 May '42 (33)	192 pts. → 117 → 75	Essentially Hyman technic Mapharsen-150-400 mg/day 9-12 hrs. injection Arsenotherapy Alone 5 days Arsenotherapy + typhoid or malaria	Primary & secondary fever; peripheral neuritis, toxicodermas. Headache, nausea and vomiting. No serious or late toxic complications. 5-8 paroxysms in 75 pts. No fatalities.
Schoch G. & Alexander J. Arch. Derm. & Syph. 46: 128-129 July 1942 (59)	350 pts. 208 142	10 day Syringe method 120 mg. Mapharsen daily for 10 days by rapid inject. 1200 mg. Revised syst. of smaller individual doses	In the Whole group - 3 cases of hemorrhagic Encephalitis - Only 1 case resulted in death Results compare favorably with the I V drip technique.
Thomas, Werlen & Dettner Am. J. Syph. Gon. & Ven. Dis. 26: 529-556 Sept. 1942 (71)	764 pts. 280 484	Mapharsen alone .7 gm - 1.2 gm. in 6-10 days Mapharsen & Fever .54 gm - .84 gm. in 7-8 days	Cerebral reaction 1.07 % Cerebral reaction 1.03 % Reactions in this group milder. No means of anticipating Arsenical Encephalitis has been found. One death in each group due to arsenical encephalitis.

On the preceding chart, I have tried to show the main points of morbidity conclusions in the articles published from the larger case series of intensive treatments. This condensation will give a rough idea of the results obtained by a great number of investigators.

The mortality rate of routine therapy given to patients of all ages and degree of debility is less than one third that of massive dose arsenotherapy given to a slected group of young adults with early syphilis. The mortality rate for a similarly selected group under routine therapy is less than one seventh that of massive dose therapy. Furthermore the case incidence of hemorrhagic encephalitis with massive dose arsenotherapy is 60-70 times that of routine therapy. (24)

Every type and description of reaction is watched for and recorded whenever intensive treatment is used, and many reactions laid at the door of intensive methods are really drug, method and technique reactions observed but not noted in other standard treatment methods. As an example we quote the following.

Falk and Rattner observed this reaction in three cases in a series of 405 cases at Cook County Hospital.

Case I; Man 36 years of age, with an eruption of secondary syphilis, on the first day of treatment with .24 mg. of Mapharsen, immediately after withdrawl of the needle from the vein, complained of constricting pain in the chest, especially severe in the precordial area. The pulse rate was 64, the respirations forced and rapid and the heart tones diminished. Treatment with Morphine Sulfate afforded quick relief, and arsenotherapy was continued without any further reoccurrence of pain.

Case II; A man 29 years of age, with an eruption of secondary syphilis, experienced similar symptoms at the end of the second day of treatment. He complained in addition of severe tightness in the abdomen. He responded to treatment with atropine alone, and treatment with arsenic was continued uneventfully.

Case III; A woman 26 years of age, receiving a second five day course of arsenotherapy because of a serologic relapse, experienced similar symptoms, but to a milder degree, which likewise subsided after injection of atropine sulfate. She had not experienced such symptoms during the first course of treatment four months previously, although she had been restless and complained of pain in the arm and nausea throughout both courses.

Prats, Varas and Haraszti previously reported on two cases of precordial oppression occuring during arsenotherapy. (17)

Hemorrhagic encephalitis due to arsphenamine treatment is a very severe condition, coming on fairly rapidly within a few hours or days of administration, characterized by edema of the brain, capillary engorgement, and minute hemorrhages. The patient becomes drowsy, apathetic, delerious, noisy, then comatose with stertorous breathing, almost as in the case of alcoholic wet brain. A convulsion may occur. Death may ensue within 48 hours. Immediate injection of 5 to 10 minims of 1:1000 adrenilin solution intravenously. repeated every few hours if necessary, may save life. Hypertonic solutions (100 c.c. of 10% saline or 25% sucrose) should also be given intravenously, followed by sodium thiosulphate. (63)

Two of the most alarming reactions which have followed the intensive arsenotherapy of syphilis are, hemorrhagic encephalitis and peripheral neuritis. With neoarsphenamine, hemorrhagic encephalitis occurred twice in ill patients and in one instance proved fatal. In the entire group treated with Mapharsen, both by continuous drip, and multiple dose methods; the incidence of hemorrhagic encephalitis was approximately 1 per hundred patients treated and the mortality from this

complication was approximately 1 per 300 patients.

Another serious reaction following the "five day" treatment is peripheral neuritis, which occurred among 35 per cent of the patients who received neo-arsphenamine and among 8 per cent of the 968 cases receiving Mapharsen collected by Elliott and his co-workers. Among the former group it was generally severe and occasionally resulted in permanent disability. Among those receiving Mapharsen it was relatively mild with no permanent sequelae reported.

Of the other treatment reactions, the toxicodermas which occurred in approximately 45% of the patients treated with neo-arsphenamine and in about 10-12% of those treated with Mapharsen are of interest because of their frequency. These reactions, generally preceeded or accompanied by fever, seem analogous to erythema of the ninth day. (44)

VII

"Sociologic aspects"

If it were possible to divide the country into halves, isolating all syphilitics on one side and those free of syphilis on the other, and by gradual treatment render the syphilitics free of the disease before allowing them to mingle with those who are not infected until the disease had been eradicated there would be no necessity for finding new methods of treatment, our old ones would suffice.

Since it is impossible to create a situation of this kind, we must grope for other methods of obtaining the same result.

Most people are familiar with the past methods of treatment. They realize that such methods are time consuming at best, and that constant medical supervision is necessary. As a consequence, those conscientious persons who will follow through a scheduled method of treatment are few and the result is that many infectious persons are left at large to spread the disease.

Most people do not object to a short period of hospitalization, especially when the majority of the expense is borne by others. For this reason there is a true social value in an intensive method of treatment.

At the present time, a number of free clinics

employing intensive methods are scattered throughout the country, and from reports they have submitted, they have no difficulty in finding patients. This proves the point that people are really cognizant of the fact that syphilis is detrimental to their health, and do wish to rid themselves of the disease. It also proves that the biggest draw back to medical eradication of the disease is the present slow treatment method.

We can safely say, that if the newer methods of treatment can accomplish the results we hope for, the time is not too far in the future, when we will be able to wipe the name syphilis from the medical lists of the country, just as surely as if we were able to accomplish the seggregation mentioned in the first paragraph of this section.

Such an accomplishment would be of social benefit for it would add man hours to industry; increase the health ratio of the race; and raise the standard of living of syphilis infested communities. The incidence of premature deaths from the ravages of late syphilis would also give us many brilliant minds lost to the world by the ravages of the spirochete.

VIII

"Summary and conclusions"

In summarizing our investigation of intensive treatment we may say, that much is yet to be expected in the way of development.

We have seen, that a firm historical foundation has been built for its use, as must be present in any radical departure from present methods.

Pharmacologic investigation has developed new or improved drugs which are being used in this treatment method, and which seem ideally designed for it.

An experimental groundwork has been laid in laboratory and clinic to provide a working basis for the promotion of better techniques.

It has a true sociologic aspect, and much is to be gained in this field.

As to the method which will eventually find universal use, it is hard to say at this time, if that method has as yet been tried. Through the use of penicillin, although this paper does not contain extensive investigation into its use, as such information is not yet available , we hope, because of its simplicity in use, and its efficacy in treating other diseases, that it will eventually prove to be the really effective means of eradicating syphilis.

This is a relatively new concept, and as such has far to go before the ultimate goal is reached,

but in evaluating the work done up to the present time, I think we may safely say, that on an experimental basis, intensive treatment, properly conducted is very effective, not unreasonably dangerous, and should be used extensively if its administration can be adequately supervised by experts in the field.

We have seen through this article, the prominence played by the expression, "time dose relationship." Using the time dose relationship principle, a large number of variations of the intensive treatment method have been tried. They range all of the way from one day of combined fever and arsenical treatment to six months of combined arsenical and bismuth treatment. Frankly no one knows yet what will prove to be the best combination of time and dose, nor whether fever or bismuth or both will find a place in the optimum method. One thing seems reasonably certain, that after some years of careful study a method of treatment which is much quicker than the present standard "one year plus" method will become available.

At present the longest of the quick methods, namely twenty six weeks of treatment with combined Mapharsen and bismuth seems the safest and at the same time an effective method of treatment of early syphilis. Many clinics now employ this method.

Lay people are often impatient with the medical profession for what seems undue caution in the matter of treatment of syphilis. It should be remembered that all ofthe articles written in the various current publications, which now hold the spotlight of popularity, do not always carry articles by recognized leaders in medical fields. It is the tendency of these articles to capture public opinion by having a rather melodramatic flare, which will capture the imagination and draw impossible pictures of present day methods of treatment, praising their simplicity of administration and availability to the people in general. Such is, however, not the case. The magazine articles tried and true treatment is often still in experimental phases and is as yet not ready for general public consumption.

Syphilis is a very slow acting disease, and its worst effects may appear ten to thirty years after infection. It is this fact that physicians must consider in evaluating new methods of treatment. Mere disappearance of the signs of the disease on the skin and mucous membranes, a single negative blood test, are far from a guarantee that the disease has been eliminated from the body. Physicians know fairly well what the old standard methods will accomplish

with maximum safety and comparatively small inconvenience to the patient because we have had about thirty years of experience with these methods. We should not be chided for taking a conservative attitude regarding methods with which we have had only a relatively few years of experience. We are dealing with human life, and in such a capacity, we cannot afford to take chances. When we accept a method of treatment as standard, we must be sure of its capabilities, mortality and morbidity rate and clinical results, otherwise, we are dealing with potential death.

IX

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