SYPHILIS

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THE TREATMENT OF EARLY AND LATENT SYPHILIS

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The best approach to the modern treatment of early syphilis is a series of short, and to some extent disputable statements indicating landmarks in the progress of the past 35 years. This summary is substituted for the narrative type of historical perspective in this review.

The Mercurial Era. Syphilis therapy up to 1912 left the disease to pursue its physiopathologic course comparatively little influenced at least by the milder and hence most popular forms of medication—the therapy *per os* of the widely copied French school. Even mercury intramuscularly except as the water-soluble salts, and the violently reaction-producing calomel veneered the surface of a syphilitic infection rather than attacked its roots.

The Early Arsphenamine Era. The "therapia sterilisans" period or 1-dose cure era promised by Ehrlich's theorization slowly changed under the impact of criticism from older observers of the course of syphilis under treatment. The belief that something radical, time-saving and treatment-shortening had been accomplished by "606" died hard. One dose was succeeded by successive doses as experience grew. Relatively new conceptions of "cure by stage" came into existence with curious incomprehensible offshoots such as the doctrine of chancre-excision. "Abortive cure," essentially the systematic speculative underestimation of the amount of treatment required by the seronegative primary stage, dates back to this era. From 1916 to 1919 the "course" conceptions of syphilis treatment established themselves, together with a combined theoretical and speculative discussion of the necessity for and the appropriate use of arsphenamine and heavy metal.

The Early Evaluative Period. From 1919 to 1922, an extensive literature, unfortunately not too familiar to some claimants for priorities, constituted the initial "shake-down" of an accumulating experiential tradi-

tion. While limited to the serologic effects of treatment and the occurrence of grossly visible forms of relapse as criteria for determining effects, many of the outlines along which the new era has developed were foreshadowed by the reports of Gennerich,[17] the German Dermatological Society (Rost, 1921,[40] Almkvist,[1] Bering,[4] Boas,[7] Hoffmann,[21] Bruck,[9] Jadassohn,[24] Ullmann,[47] Eicke,[15] Hoffmann-Mergelsberg,[22] Müllern-Aspegren,[33] Haxthausen,[20] Rasch,[38] Scholtz[Silberstein[42]], Satke,[41] Mutschler,[34] Zieler,[50] Bruns,[10] Riecke,[39] Bernard,[5] Harrison[19] and others). The stage-of-beginning treatment conception received more or less precise delineation towards the latter part of 1922. A type of foreshortened intensified therapy, that of Scholtz, was reported by Silberstein[42] in 1923, before any American contributions were in the field. When American studies did appear, however, they rapidly established a series of important conceptions, beginning with Moore and Kemp's[31] demonstration based on Keidel's[20] foresighted Johns Hopkins system, of the importance of continuity in treatment, and S. W. Becker's[2] demonstration at the Mayo Clinic of the value of massing or intensification of arsenical therapy at the moment treatment is begun. Familiar to Americans during this period are the Pollitzer-Ormsby[35,37] variation on the Scholtz technic and other types of intermittent systems which lost ground after the League of Nations confirmation[28,46] of the substantial superiority of continuous treatment.

The League of Nations Syphilis Commission Evaluations.* Begun on a massive scale in 1928 with conclusions and recommendations stated in 1935, this world-wide survey of technical methods in the treatment of early syphilis provides the basis for what may now be spoken of as the conservative or prolonged method for the treatment of early and latent syphilis. Under the terms of the coöperative agreement among the nations participating, each was individually encouraged to make the most of his own material in addition to contributing to the general pool. This rapidly brought American material into the foreground, and the contributions of the Cooperative Clinical Group[13] working under the ægis and with the statistical coöperation of the United States Public Health Service, express today what might be called the basic formula of American practice. From the League of Nations evaluation for which Martenstein supervised the interpretations,[28] two general systems of treating early syphilis emerged —the British-Scandinavian intermittent and the American continuous systems. A certain amount of argument has inevitably arisen over the suitability of the material for deciding the question of intermittence *versus* continuity, but on the whole the Commission's findings seemed to justify the belief that the intermittence of the recommended intermittent system is more formal than actual and that its intensity especially in simultaneous arsenical and heavy metal administration, causes its effects to be substantially those of a somewhat less intensive but continuous technic. Enthusiasm for the newer foreshortened procedures (see below) should not be allowed to dim the significance of this great evaluative accomplishment, and the syphilologist of today may without hesitation subscribe to either of the announced conservative systems as the equal in curative

* Under the direction of the League of Nations Health Organization, the following countries participated: Denmark, France, Germany, Great Britain, United States of America. The membership in 1928 included Jadassohn (Breslau), Chairman, Madsen (Copenhagen), Colonel Harrison (London), Queyrat (Paris), Stokes (Philadelphia), Rasch (Copenhagen); Gougerot replaced Queyrat, Lomholt replaced Rasch in 1935. Statistical consultant, Westergaard (Copenhagen). Evaluation and report by Martenstein (Dresden).

effect of the more recent "hurry-up" systems of procedure with a substantially greater margin of safety.

Since the League of Nations evaluation has established such substantial landmarks, it may well be used as a milestone at which to summarize the high points of the progress of syphilotherapy since the close of the mercurial age. The following fundamental principles have emerged from a quarter century of revolutionary progress:

1. *Early and not late syphilis is the domain of systems.* Bad effects follow haphazardness, short courses, low dosage and lapse from treatment in early syphilis.

2. The "*stage at which treatment is begun*" *principle* is established with trustworthy evidence that seronegative primary syphilis is the most easily cured of all stages of the disease, seropositive primary syphilis the most uncertain or resistant and secondary syphilis midway between the two.

3. *Relapse follows short treatment,* especially arsenical, producing delayed secondaries, neurorecurrence, infectious mucosal lesions, serologic relapse and fastness.

4. *Single drug treatment is inferior to combined treatment* and a heavy metal improves arsenical results and compensates shortcomings.

5. *Prolongation*—more injections, longer courses—gives superior results in systems dominated by the calendar interval of 1 week. Prolongation and increased mass through individual and total dosage were, of course, attempts to meet the resistance of the 30% relapsing group among early syphilitics at large.

6. *Dosage theory* was spotted with empiricism. The concept of lower drug tolerance of the female as compared with the male; the large *versus* small dose school; the crowding or time-dose problems represented by the so-called intensive method; the toxicity fears (simultaneous *versus* alternate administration of arsenical and heavy metal); the idiosyncrasy and technical error factors in reaction interpretation which held down dosage, while reports of relapse and resistance raised it.

7. *Calendar servitude* or the domination of the 7-day interval on a purely empirical unevaluated basis was general. Few ventured to think in terms of shorter intervals or would admit their practicality or desirability.

8. *Rising appreciation of scheduling.* It became clear that schedules or systems critically examined by large syphilologic centers and expert experience were the sound basis for treatment methods rather than the results of blood serologic tests, thus slowly displacing the serologism of the 1920's.

9. *The vital comprehension of toxicity and therapeutic efficiency relations* was dominated by the laboratory and rested on the insecure foundation of trypanosomiasis in mice rather than syphilis in man or animals. This group of conceptions, though expressed by impressive numerical indices was essentially vague and inadequate. A true experimental basis for syphilotherapeusis did not yet exist.

10. *Despite these strictures on the knowledge of the day,* the work of individual investigators plus the League of Nations evaluations established the following facts:

(*a*) *An arsphenamine alone can "cure" early syphilis* in a large percentage of cases.[27]

(*b*) *Heavy metal is a potent augmenting force,* particularly true of bismuth; a fact recently "re-discovered" by recent workers with intensive methods.

(*c*) *Arsenical therapy can be "crowded"* or "foreshortened" without fatal effect and with good results (Scholtz-Silberstein massive divided dose system).

(*d*) *Continuity and calendar regularity* are vitally important to the conservative or prolonged systems evaluated by the League of Nations. "A little treatment continuously given is twice as effective as the same amount of treatment intermittently given."

(*e*) *Prolongation of treatment* (in the weekly calendar or conservative systems) irons out most complications, relapse and resistance.[3]

(*f*) *Some important League of Nations and Cooperative Clinical Group principles:*

(1) The curative outlook is one-third better when treatment is begun in the seronegative primary stage than in other stages of early and and latent syphilis.

(2) The good results obtained by prolonging continuous treatment longer than 1 year more than double those obtained by the same kind of treatment carried through less than a year.

(3) Intermittent and irregular treatment are the principal sources of delayed reversal of the blood serologic reaction.

(4) Prolongation and intensification of treatment, using much arsphenamine and heavy metal, but especially much arsphenamine in the first 3 months promotes good results.

(5) Satisfactory results may occur with little treatment, but much treatment and over prolonged periods is twice as effective as little treatment if continuously applied, and 5 times as effective as treatment intermittently applied.

(6) Arsphenamine is the chief factor in relapse prevention, and this applies specifically to the incidence of neurosyphilis (note importance of this principle in foreshortened intensive methods).

(7) Serologic irreversibility becomes the more marked the later in early syphilis treatment is begun, and the more frequently lapse from continuity occurs whether in the form of rest intervals or otherwise.

(8) A weak positive serologic reaction interrupting a series of negatives in early syphilis is a distinct warning of the possibility of relapse.

Much of the effectiveness of the foreshortened intensive treatment methods was predicted by Martenstein's conclusions from the general League of Nations material that the employment of a comparatively heavy individual dosage of the arsenical and of bismuth or mercury with administration in rapid succession at the outset of treatment, leads to superior results. Furthermore, approximately the same amount of treatment should be administered to primary as to secondary cases.

(*g*) *Large dosage is preferable to small;* should follow a weight standard, and be without sex differentiation.

(*h*) *Many of the most serious complications of treatment* are due to background causes (idiosyncratic-allergic, intercurrent infections, and technical factors rather than the drugs as such alone). In particular, the combination of arsenic and bismuth is as safe as arsenic alone.

(*i*) *To date, no claims for the use of a heavy metal alone* in the treatment of early syphilis have withstood critical evaluation. An arsenical is essential as a controller of infectiousness. The effect is augmented by bismuth, and also though probably less so, by mercury. Twenty full doses each of arsenical and heavy metal approximate a minimal amount of treatment for infection control (so-called 20–20 standard).

(*j*) *The controversies over the individual merits of arsenicals* (606, 914 and so forth) have been largely submerged by the overwhelming popularity of

mapharsen in American practice, due largely to its low toxicity, combined with high spirillicidal value. This has been overwhelmingly demonstrated in the 5-day massive dose arsenotherapy (5-day drip) and its therapeutic efficacy when intensively employed has also been demonstrated by the Eagle-Hogan animal experiments.

Additional Basic Principles for Present and Future Emphasis. 1. The Boeck[11] material underlies the principle that *syphilis "cures" itself* in 40% of cases.

2. A little treatment in early syphilis[36] raises the percentage of cure another 20% to 30%.

3. *Intensification and prolongation* (or repetition in the case of intensive foreshortened methods) directed at the resistant 30% bags another 15% to 25%, depending on stage-of-beginning-treatment, for cure.

4. *The remaining 5% to 15%* represents the irreducible residue of resistance (deficient defense, special strains and so forth) that nothing save time, therapeutic repetition and variation, and fever, if anything, will cure.

5. *Non-specific agents* (fever) have important re-enforcing and curative effects in early as well as late syphilis—chiefly by enhancing the effectiveness of arsenicals faster than it increases their toxicity.[6]

6. *The spinal fluid examination* is an indispensable evaluative and curative check procedure more important ultimately than blood serology.

7. *As to observation and discharge as cured,* all patients who have had an entirely non-relapsing course while receiving ideal treatment should be informed that a cardiovascular reëxamination in the 5- to 10-year period is necessary.

8. *The syphilitic pregnant woman* or the woman who has had syphilis and is believed to be cured should have her status reviewed with every pregnancy and safety-first requires her treatment for protection of the child during each pregnancy whether seronegative or seropositive.

9. *Unsatisfactory results* (non-cure) are usually reviewed by the 5th year of observation and Padget found no less satisfactory results in any case after 10 or more years of observation.

Principles Established by the Clinical and Experimental Study of Foreshortened Intensive Methods. The past decade of work with intensive treatment methods has contributed a number of additional important principles to our understanding of syphilotherapy.

1. Hyman and his co-workers[16] have demonstrated that an approximation to the *total curative dose of an arsenical can be administered to a human being* by an intravenous infusion method (drip) without necessarily disastrous effects with a controllable though increased toxicity and with satisfactory results.

2. *A toxicity-therapeutic efficacy relationship* has been worked out by Eagle and Hogan[14,16] on the basis of animal, and more recently human clinical results. Syphilis can be cured in 80% to 100% of cases (stage-of-beginning-treatment factor) by a total dose of 20 to 30 mg. per kilo body weight of an arsenoxide (mapharsen) alone.

3. *The toxicity of such a dose* is inversely proportional to the time in which this dose is given.

4. *Any combination of toxicity and time relationship* (that is, any margin of safety) that practical considerations may dictate is theoretically possible, the mortality rising with the shortening of the time in which the total dose is delivered.

5. *The addition of bismuth* ("re-discovery") *greatly enhances the effect* of

all foreshortened intensive arsenotherapy (informally estimated by Eagle as 8 times better effect with bismuth than without).

6. *Serologic signs and symptoms* under foreshortened procedure disappear gradually on a now well-recognized gradient to which a quantitative serologic procedure is essential in interpretation.

7. *A wide variety of time and technical variations* (5-day intravenous drip *versus* 10-day multiple injection, *versus* 10 to 12 weeks of 2 to 3 injections weekly, *versus* 26-week schedules) with graded morbidity and mortality but substantially identical therapeutic outcome can be employed as forms of "foreshortened intensive" systems in the name of various types of exigency or expediency.

8. *The mortality of the 5-day drip* is currently estimated at 1:200 to 1:300. Any schedule completed in 20 days or less will have a mortality greater than 1:1000 (Eagle-Hogan); 10- to 12-week systems have a mortality of approximately 1:1500. The mortality of 20- and 26-week systems is not yet definitely known. That of reasonably good performance of the standard conservative prolonged systems is estimated by Hahn[18] (Johns Hopkins Hospital) at 1:1950; with optimum experience at 1:2800. It must be recalled that the mortality of conservative treatment is computed from arsphenamine and not mapharsen-treated cases. The toxicity of mapharsen is so low (1 death in 3938 patients[16]), that a material drop in mortality should follow its use in the conservative systems. Levine and Keddie estimate the mapharsen death rate to be $\frac{1}{2}$ that from neoarsphenamine.

9. *The foreshortened intensive procedures* (up to 12 weeks) greatly reduce the incidence of neurosyphilis.

10. *The justification of the foreshortened procedures* except for their apparent efficacy in the prevention of neurosyphilis (spinal fluid abnormality) is in the main still one of emergency and expediency. The ultimate results are obtainable by the older slower methods with less risk of life. What effect this will have on their post-war use remains to be seen.

In a discussion of the basic principles of system evaluation applicable to foreshortened intensive methods, Stokes[43c] wrote as follows:

"Any new systems proposed should be judged basically by their ability (*a*) to equal or surpass the 'curative' expectancy of the old ones; (*b*) to lead to less infectious relapse; (*c*) to reduce the incidence of cardiovascular and neurosyphilis, and (*d*) by their relative risks to the patient.

"For the evaluation of a system, time and observation are necessary to establish reduction of, or absence of relapse and progression. For the former, 2 to 4 years; for the latter, up to 10 years is a reasonable observational requirement. For decision on relapse the patient must be repeatedly and frequently observed, for it is a come and go affair. For the evaluation of 'cure,' from a decade to a lifetime, the longer the better, is required.

"A system which under such scrutiny has shown itself at least equal to its predecessors may then proceed to claim additional advantage and support for a variety of reasons, including cheapness, rapidity, controllability of the lapse factor because the whole job is finished in a short time, aid in the widening of availability of treatment by making possible the treatment of more persons per unit of time, personnel and equipment. Such considerations are in the main secondary to those of control of infectiousness and real curative power.

"If the new system equals the old or surpasses it in all these particulars it has but one more hurdle to make before achieving priority. While

primum non nocere is losing some of its meaning in a war-torn world, there are still arch conservatives who are inclined to examine critically the bad effects, the complications of a system. Of real importance to the victim are the risks involved, the chances of damage or of death from treatment in the case of a disease which with none or very little treatment gives the victim at the outset a 40 to 70% chance of escape from serious consequences. If an equal chance of escape with an older method offering less risk exists, only the most cogent reasons and a free choice by the patient of the more dangerous method justify its election."

The Conservative or Prolonged Standards of Treatment for Early, Early Latent and Late Latent Syphilis. It is now in order to summarize what may be called the "official" or most widely authenticated and accepted systems for use in that phase of the disease which permits of systematization in procedure. While it is impossible, with the rapid changes taking place in syphilotherapy, to predict how long such systems will have a following, it should be clearly understood that they are effective, and will do all that the foreshortened systems will, with a very much greater margin of safety. To the British-Scandinavian intermittent system[8] (which must be exactly followed, diagram in hand) and a slight but now, for American practice, "official" modification of the American continuous (League of Nations) system, the "30–60–03,"[43] is added the as yet unproved and unevaluated but rational "Army Plan" recommended to the Surgeons General by the National Research Council and publicized in Circular Letter No. 74. The conservative systems are still, we believe, the backbone of modern practice, the basis of much of our present knowledge of mechanism and effects, and likely to be displaced completely only by certain radical changes in the whole chemotherapeutic attack on the disease such as are affecting the pyogenic infections, gonorrhea, etc. (the sulfonamides, penicillin).

The British-Scandinavian (League of Nations) System: Plan of Courses of Injection.

A course consists of 8 weekly injections of neoarsphenamine (0.6 to 0.75 gm. each) or arsphenamine (0.4 to 0.5 gm. each) given simultaneously with 8 weekly injections of an insoluble bismuth compound (0.2 to 0.24 gm. bismuth metal each) and followed by 2 more weekly injections of bismuth compound. An equivalent amount of a mercury preparation may be substituted for the bismuth (inunctions for 40 days at 3 gm. of unguentum hydrargyri or injections of 70 mg. of mild mercurous chloride or 120 mg. of mercuric salicylate, etc., suspended in a suitable base). It is recommended that:

(*a*) In cases which remain or become serologically negative during or by the end of the first course, 4 such courses be administered, with intervals of 3 to 5 weeks between any 2 courses.

(*b*) In cases which have not become seronegative by the end of the first course, in addition to the amount of treatment shown in (*a*), further courses should be administered until the patient has received as a minimum 3 beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary.

(*c*) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (*b*).

For non-pregnant females, treatment should be administered on the plan outlined for men, with the exception that the single dose of neoarsphenamine should be reduced by 0.15 gm. and that of arsphenamine by 0.1 gm.

In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the intervals.

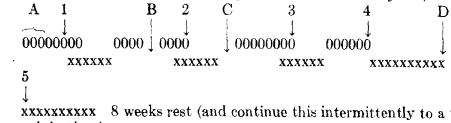
The American Continuous System: The "30–60–03" "Official" Modification, Circular Letter No. 18 of the Surgeon General's Office, U. S. Army. The published work of the United States Public Health Service and the Cooperative Clinical Group in the United States has indicated that continuous treatment with an effective arsenical alternating with bismuth on a definitely defined schedule with calendar regularity and without rest periods during the arsenical phase is the optimum conservative technic for the treatment of seronegative and seropositive primary syphilis, secondary syphilis, and early latency (within the first 4 years of the infection when the duration is known). An essentially similar standard of treatment employing 606, parallel with an acceptable intermittent (British-Scandinavian) system of treatment employing neoarsphenamine, has been recommended by the Commission on Syphilis and Cognate Subjects of the League of Nations as a result of an extended study of an international statistical material. It may therefore, it is believed, be accepted as having the support of authority.

For mnemonic convenience, the designation, "30–60–03" is suggested, for the standard system for early and early latent syphilis;[43] the "30" representing the number of arsenical injections; the "60" representing the number of weeks of bismuth therapy, equivalent to 60 injections of bismuth subsalicylate, and the "0" and "3" representing respectively, no rest periods, and 3 years of combined treatment observation. By "treatment observation" is meant the total elapsed time from the institution of treatment in accordance with this schedule until the patient is discharged from observation as presumptively cured.

Since the sequence of various types of treatment in this system, the prevention of relapse by overlapping of heavy metal and arsenical therapy, the serologic controls, the spinal fluid examination, all are integral parts of the treatment system, the following diagram is offered as presenting these various relationships.

The "30–60–03" for Early Syphilis.

30 neoarsphenamine or mapharsen injections, 60 weeks of bismuth injections.
NO rest intervals in the arsenical phase, 3 years of treatment observation.
0 = neoarsphenamine or mapharsen; x = bismuth subsalicylate; weekly intervals.



A = first 3 injections compressible into 10 to 14 days. Some risk of increased reactivity.
B = average case seronegative, 16th week.
C = Examine spinal fluid if blood is still positive, 24th week.
D = Always insist on spinal fluid examination before rest period.
1 = if blood test has become negative, suspect low resistance.
2, 3, 4, 5 = if weak positives appear among negatives, suspect relapse, neurosyphilis.

The "30–60–03" schedule as thus presented can be drawn up in "vertical" as distinguished from the above "horizontal" arrangement, week by week, for printing directly on record forms.

The published observation of the USPHS–CCG group on the treatment of early syphilis indicated that the "30–60–03" schedule could be most effectively applied to seronegative primary syphilis and fully developed secondary syphilis. In the case of seropositive primary syphilis, whose status should be confirmed in the seronegative cases by a repetition of the blood test on the day following the first

arsenical injection, there were definite indications that the seropositive primary phase of the disease, lacking the development of a full-fledged immunity reaction on the part of the body was the most resistant to cure, and the most prone to relapse of the 3 groups of cases included under the designation, "early syphilis." It has accordingly been proposed that in seropositive primary syphilis and initially negative primary syphilis which becomes seropositive on the blood immediately following the institution of treatment, a "40-80-04" system be employed, meaning thereby an additional 10 arsenical injections and 20 bismuth injections and another year of observation over and above the standards proposed as generally applicable to early and early latent syphilis. This extension of the arsenical phase of treatment can take the form of 5 courses of the arsenical of 8 injections each, in place of the 3 courses of 8 and 1 course of 6 injections in the "30-60-03" system. The bismuth therapy may follow the usual 2-injection overlap, plus 4 additional injections in the arsenical intermission that is employed in the "30-60-03"; the remaining bismuth injections to complete the 80-week standard, being continued in 10-injection intermittent courses after the completion of the arsenical phase of treatment.

The 26-Week Army System. The diagram is adapted from Circular Letter No. 74, Surgeon General's Office, U. S. Army.

Week	Arsenoxide	Week	Bismuth
2		1	
2		2	Bismuth subsalicylate intramuscularly once a week, 5 injections
3		3	
4	Arsenoxide intravenously twice a week; total 20 injections	4	
5		5	
6		6	Omit bismuth subsalicylate 5 weeks
7		7	
8		8	
9		9	
10		10	
11		11	
12		12	
13	Omit arsenoxide 6 weeks	13	Bismuth subsalicylate once a week, 6 injections
14		14	
15		15	
16		16	
17		17	
18		18	Omit bismuth subsalicylate 5 weeks
19		19	
20	Arsenoxide as in first course twice a week; total, 20 injections	20	
21		21	
22		22	
23		23	Bismuth subsalicylate once a week, 5 injections
24		24	
25		25	
26		26	

Dosage. Arsenoxide, 0.05 to 0.07 gm., based on patient's weight. Bismuth subsalicylate, 0.2 gm. (Forty injections arsenoxide—16 bismuth subsalicylate.)

Serologic Control of Treatment. In patients with early syphilis treated with the Army system, a serologic test will be done at the beginning and end of the schedule of treatment outlined but treatment may be stopped whether the serologic reaction for syphilis is positive or negative. After the completion of treatment the serologic tests should be repeated 3 and 6 months later. If the reaction is negative after 6 months, the case may be classified as "result satisfactory" and the *Syphilis Register* may be closed. If the test is positive after 6 months, the patient should be referred to a station or general hospital.

In patients with latent syphilis the serologic tests should be repeated at the completion of the treatment outlined, but the *Syphilis Register* may be closed when this treatment is completed, regardless of the result of the serologic test.

Spinal fluid examination should be performed in a hospital in patients with early syphilis at the end of the course of treatment outlined, or as soon as possible there-

after, but in any event before the *Syphilis Register* is closed. In apparent latent syphilis, spinal fluid examination should be performed in a hospital before treatment or as soon as possible thereafter, but in any event before the *Syphilis Register* is closed.

A System of Treatment for Latency—"24–60–100 plus." Before defining a system by which adequate treatment of latency may be judged, it must be reëmphasized here that the latency implied is "monosymptomatic seropositive latency" in which absolutely no clinical evidence of syphilis can be identified on complete physical examination except the positive and confirmed—and confirmable—blood-serologic reaction for the disease. An adequate examination of the spinal fluid is necessary to establish the fact that a seeming latency is not complicated by asymptomatic neurosyphilis. A patient who has been adequately treated for an early syphilitic infection but who still remains seropositive on the blood in order to be considered as in monosymptomatic seropositive latency (serologically fast) should have had a negative spinal fluid 1 year after the close of his treatment for early syphilis, and if more than a year has elapsed since the cessation of such treatment, a repetition of the spinal fluid examination is desirable. A long series of negative spinal fluids is not necessary to the establishment of the status of monosymptomatic seropositive latency, for according to USPHS-CCG observation, more than 1 or 2 repetitions of a negative fluid in the absence of any developing clinical signs is unnecessary.

The latency of a syphilitic infection is divided arbitrarily into an early and a late period, partly because of the greater risk of infectious relapse and other types of recurrence in early latency, and partly because of the presumed better outlook for complete arrest if not cure in the earlier years of the latent period. The dividing line between early and late latency has tended in American practice to be the fourth year of the disease. This is an arbitrary setting which may in the judgment of an expert, be varied one way or the other. A young and robust person whose infection is of 5 or even 6 years presumed duration may be advised to accept the standard for an early infection in his treatment. On the other hand most genuine latency, after the 4th year, shows relatively little tendency to progression, and may be treated by a standard substantially lower than that proposed for the radical cure of early infection.

The treatment of early latency (first 4 years of the disease) is that of early syphilis—the "30–60–03" system.

The Cooperative Clinical Group's[13] experience has indicated that for the treatment of late latency (after the 4th year) 3 courses of 8 injections each of an effective arsenical given in continuity and alternation with 10 injections of bismuth subsalicylate, without overlap and with continuity extending only through the arsenical phase, constitute an adequate beginning. The continuous treatment with arsenical and heavy metal is then followed by an intermittent and prolonged treatment with bismuth alone which should total, including the three 10-injection bismuth courses given with the arsenical phase, not less than 60 weeks of bismuth therapy. Further treatment with bismuth to the extent of 80 weeks, or even 100 weeks, or on the basis of 80 weeks, plus "a course a year" for several years, was found to increase appreciably the good results by the criteria employed. It is not necessary, however, in judging candidates for admission to the services, to insist on prolongation of the heavy metal phase beyond the 60th week. Approximately 70% of monosymptomatic seropositive latency may be expected to reverse to negative on the blood for an indefi-

nite period following a 24–60 course, and the failure of the remaining 30% to reverse may be regarded as no bar to eligibility.

As a general principle, late latent cases remaining seropositive after a 24–60 course should be observed at intervals of a year or two with physical examination and appropriate tests for evidence of cardiovascular progression and ultimate neurosyphilitic involvement.

It should be emphasized that late latency is usually much overtreated on the basis of fluctuating positive blood serologic reactions alone, or because of conflicts between the results of various laboratories ("serologic discord").

Massive Dose, Foreshortened Chemotherapy of Eealy Syphilis, Description of Procedure, Indications and Contraindications. All methods of intensive therapy are intended for patients with early syphilis (primary, secondary, relapsing secondary, and early latency) who have received little or no previous therapy, who are robust young people, especially men, reasonably free from serious visceral disease, particularly hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, and history of previous serious arsenical reaction. Although it is safe to administer sulfonamides simultaneously with conservative prolonged therapy and even with the 12-week system, it is unsafe to give sulfonamide therapy for gonorrhea or other conditions to patients receiving 5- to 10-day intensive therapy.

Pre-treatment Routine (All Methods of Intensive Chemotherapy) (after Leifer, 1940[16]). The routine examination consists of the following: 1. Daily urinalysis, including determination of urobilin.

2. Determination of the urea nitrogen content of the blood and the icterus index.

3. Complete blood count, including that of the platelets.

4. Complete physical examination on admission.

5. Serologic examinations made in 3 different laboratories (these include the Kolmer, Kline diagnostic, Kline exclusion, Kahn standard and titered Wassermann tests).

6. Dark-field examination of material from all open sores.

7. Estimation of renal function by determination of the specific gravity of the urine.

8. Special tests of hepatic function by the bilirubin method.

9. Studies of the excretion of arsenic in the urine and in the stool and its concentration in the blood (optional; for study purposes).

Technic of 5-Day Intravenous Drip (Chargin, Hyman, Leifer[16]) (after Committee on Massive Drip Intravenous Therapy, 1940). *Materials:* 1. Needle—deep injection type, No. 20, $1\frac{1}{2}$ inch length.

2. Diluent—5% dextrose solution.

3. Drug—mapharsen (arsenoxide), ampoules 0.04, 0.06, and 0.06 gm.

4. Glass gravity cylinder, 300 cc. capacity with attached rubber tubing, glass drip chamber, adapter for needle. Vacoliter or similar container may be used instead of apparatus described (L. W. Shaffer).

5. Adhesive or Scotch tape ($\frac{1}{2}$ inch width).

Dosage of Mapharsen: 1. Total dosage for the 5-day treatment period is determined by the stripped weight of the patient. In patients weighing less than 70 kg. (155 pounds) the total dose is 1000 mg. (1 gm.); in those weighing 70 kg. or more, the total dose of mapharsen is 1200 mg. (1.2 gm.).

2. The daily dose is 200 mg. (0.2 gm.) for patients receiving a total of 1000 mg. (1 gm.).

3. The daily dose is 240 mg. (0.24 gm.) for patients receiving a total of 1200 mg. (1.2 gm.).

4. If a patient receives less than the intended daily dose (this will most often occur on the first day of therapy), the deficiency in dosage may then be spread over the remaining days of treatment. Thus, if the patient receives 120 mg. (0.12 gm.)

the first day instead of the intended total daily dosage of 240 mg. (0.24 gm.) he may be given 30 mg. (0.03 gm.) additional on each of the succeeding 4 days of treatment.

Procedure: Site of Election for Insertion of Needle. After cleansing of forearm and application of a tourniquet above the elbow to distend the veins, the needle is attached to a 2 cc. Luer type syringe and inserted in a vein on the forearm, usually anterior or outer aspect, between elbow and wrist, to allow movement at these articulations. Needle should be inserted into vein up to the hub, a gauze sponge placed beneath the needle hub, and the needle fixed in place with adhesive (or Scotch) tape. Alternate arms used on succeeding days.

The adapter of the intravenous set is attached to the needle (after the adapter has been freed of air bubbles) after the removal of the tourniquet, and the solution is allowed to flow rapidly until 10 to 15 cc. have entered. Should any swelling or infiltration be noted about the needle point, the flow should be stopped; the needle removed, and reintroduced into a different vein in the same or opposite forearm. The rate of flow is regulated by the fine adjustment clamp so that solution enters at a speed of about 50 to 60 drops per minute; thus, the entire quantity of 2000 cc. will require 8 to 12 hours for introduction.

Addition of Bismuth to Massive Dose Technic. Since July, 1941, L. W. Shaffer has been using bismuth concurrently with the arsenical. It may be used as follows:

Dosage of Bismuth With Intravenous Drip Method: 1. Suspension of bismuth subsalicylate in oil is employed.

2. The patient should receive 0.2 gm. bismuth subsalicylate (0.13 gm. bismuth metal) intramuscularly as soon as the diagnosis of early syphilis has been confirmed.

3. The second dose of 0.2 gm. should be given on the 3d day of treatment, the third dose of 0.2 gm. on the 6th day and a fourth dose of 0.2 gm. on the 9th day, before discharge.

Method of Preparing Arsenoxide Solutions. Mapharsen (arsenoxide), 0.01 gm., is dissolved in 100 cc. of 5% dextrose solution. Usual procedure is to prepare 500 cc. of such solution, containing 0.06 gm. mapharsen—this is enough for 3 hours of treatment.

When the Vacoliter containing 2000 cc. of 5% dextrose is used, the total daily dose of 0.24 gm. mapharsen (arsenoxide) is prepared the first thing in the morning and the solution allowed to run in, in the 10 to 12 hour treatment period.

This has been the practice in one institution. The preparation of the drug for the 10 to 12 hour period all at once has simplified the technic to a great extent.

Variants in Usual Procedure: 1. Primary fever on the 1st day (Herxheimer)—therapy is stopped if temperature reaches 101.4° F. or more. This usually happens between the 6th and 8th hour; by the time patient may only have received from 0.12 to 0.16 gm. mapharsen. The practice has been to compensate for this insufficient dose in the following manner: 1st day—0.12 gm. mapharsen (arsenoxide); 2d day—0.28 gm. mapharsen (arsenoxide); 3d day—0.28 gm. mapharsen (arsenoxide); 4th day—0.28 gm. mapharsen (arsenoxide); 5th day—0.24 gm. mapharsen (arsenoxide).

2. Clinical jaundice—when this appears in the course of treatment, the procedure should be interrupted. It has only been seen once in all cases studied (Committee report).

General Medical Care During 5-Day Intravenous Drip. Routine soapsuds enema should be given the night before treatment is begun, to obviate the need for bedpan, and whenever thereafter indicated. According to Leifer's (1940) description: "The nursing problem during the period of treatment consists of the preparation of fresh solution for each patient at the end of 2 or 3 hours and the refilling of the gravity flask. Meals are served on the ordinary bed tray. Patients can feed themselves. They are also capable of handling the urinal but, naturally, must be assisted somewhat in the use of the bedpan. The latter disturbance may be prevented by having the patient evacuate or have an enema during the evening, when treatment has been discontinued.

"The patients are given a high calory diet, rich in starches and carbohydrates. The majority of the patients read, listen to the radio, or play cards during the day In the evening, after discontinuance of therapy, they may get out of bed. They

suffer little or no discomfort. Many of them register a gain in weight of as much as 10 pounds (4.5 kg.). This gain in weight is not due to any appreciable edema but may be explained by the fact that most of these patients otherwise undernourished, are so well treated with regard to food and nursing care."

Technic of 10-Day Multiple Injection Intensive Therapy for Syphilis.[16] With this treatment system patients need not be confined to bed, but they should be treated in the hospital and observed for at least 2 days after the last injection of mapharsen (arsenoxide). Routine ward diet may be employed.

Two injections of mapharsen (arsenoxide) are given daily for a 10-day period. The injections are given in the morning and evening of each day, 10, or preferably, 12, hours apart. Schoch, however, has given single injections of 100 to 120 mg. daily as an ambulatory procedure. Dosage is governed roughly by weight. Patients weighing 50-70 kg. (110 to 154 pounds) should receive 0.05 gm. of mapharsen twice daily for 10 days. Patients weighing between 70 and 90 kg. (155 to 200 pounds) should receive 0.06 gm. of mapharsen twice daily for 10 days. The dosage may be increased to 0.070 gm. in each injection for patients weighing over 90 kg. (200 pounds). Each dose of mapharsen (arsenoxide) should be dissolved in from 8 to 10 cc. of distilled water. The *solution should be aerated* and *rapidly injected,* intravenously, promptly after preparation. In cases where solutions are made in bulk, individual doses should be given within at least a 2-hour period after preparation.

On the 1st, 4th, 8th and 12th days, 0.2 gm. of bismuth subsalicylate in oil should be injected deeply into alternate gluteal muscles.

Thomas and his associates of Bellevue Hospital combine fever therapy with the intensive multiple syringe technic (1941, 1943). The risk of serious cerebral accidents with this method increases with the amount of arsenoxide (mapharsen) given. The addition of fever does not prevent cerebral reactions but lessens their frequency by necessitating a lower dosage of arsenical.

Reactions from 5- to 10-Day Intensive Therapy and Their Management. Minor Reactions: 1. *Pain in the arm:* cold wet dressings, ice-bag, aspirin, codeine only if pain is severe.

2. *Mild headache:* aspirin or codeine usually gives prompt relief. If headache is severe, increasing and persistent, consider this as possible prodrome of toxic encephalopathy.

3. *Nausea and vomiting:* give only fluids by mouth, and sedation if necessary. If persistent, discontinue treatment temporarily. May give 5% or 10% dextrose solution alone intravenously.

4. *Primary fever:* sharp rise in temperature occurs on the 1st day of treatment especially with intravenous drip. It is usually almost normal by evening, and normal by the next day. If the temperature goes above 101.4° F. discontinue drip for the day. Next day, drip may be reinstituted, practically always without recurrence of fever; this early fever need not cause omission of the second dose when multiple syringe method is used. Primary fever is usually accompanied by a flare-up of the syphilitic lesions (Herxheimer reaction, therapeutic shock). Symptomatic treatment may be used if necessary.

5. *Secondary fever:* secondary rises of temperature in excess of 101° F. at any time after the first day of treatment are an indication for interrupting therapy because secondary fever is sometimes associated with a mild toxicoderma. Most often in the 5-day treatment the fever occurs on the last evening of therapy. Mapharsen should not be given again until the temperature is normal. If fever recurs when treatment is reinstituted, efforts at intensive therapy should be abandoned entirely.

If the patient has received at least a total of 800 mg. (0.8 gm.) of mapharsen (arsenoxide) before the appearance of fever, intensive arsenotherapy by any system should not be reinstituted. In this case all further arsenical

therapy may be omitted, but the patient should receive a total of at least 12 weekly intramuscular injections of bismuth subsalicylate before all treatment is stopped.

Symptomatic treatment for this reaction may be used, if necessary.

6. *Toxicoderma:* usually appears in the post-treatment period on the 7th day, and is often preceded by and accompanied with fever. The type is most commonly morbilliform, scarlatiniform, or urticarial, and there is no exfoliation. This is not arsenical exfoliative dermatitis, and is not a serious sensitizing reaction. The rash usually fades in $1\frac{1}{2}$ to 4 days without therapy. Symptomatic treatment may be used, when indicated.

Since this reaction does not usually occur with the intravenous drip method until all treatment has been completed, it has no bearing on interruption of such treatment. When the 10-day multiple injection system is used, the occurrence of this "9th-day erythema" is an indication for interrupting treatment. This reaction may be associated (rarely) with toxic encephalopathy, and continued treatment may increase the risk.

7. *Renal damage:* usually insignificant, consisting of minor traces of albumin, occasional red and white blood cells. No treatment is needed.

Marked albuminuria or hematuria is a signal for discontinuing treatment.

8. *Peripheral neuritis:* rarely encountered, and only in the post-treatment period. Usually manifested only by subjective symptoms, most often paresthesias. Objective changes are rarely encountered, and only sensory in type, never motor. The process disappears spontaneously. This reaction was common in the cases treated early by the 5-day method, probably because of immobility of the arm and the use of a drug too toxic (neoarsphenamine) for such a method.

9. *Nitritoid reaction:* rarely observed with multiple injections or with the intravenous drip procedure, unless the rate of flow of the latter is inordinately fast (mapharsen [arsenoxide] is well known to produce this reaction only rarely).

10. *Precordial oppression* (Falk and Rattner, 1942; Prats, Veras and Haraszti, 1942): this occurs occasionally with 5-day treatment. Disconcerting but not frequent or serious.

Major Reactions: 1. *Severe headache:* especially towards the 4th or 5th day of treatment, the occurrence of severe, persistent and increasing headache not readily relieved by aspirin or codeine should be viewed as of possible serious import (prodrome of toxic encephalopathy). It is best to discontinue intensive therapy and after a rest interval from all arsenical therapy of at least 4 weeks (this rest period to be occupied with weekly bismuth injections) to place the patient on the standard or 26-week treatment schedule, the duration of which may be shortened to the extent of the mapharsen dosage before the reaction occurred (*e. g.*, if the patient received a total of 400 mg. mapharsen before the reaction, 1200 mg. additional should be given by injections twice weekly with bismuth added as in the standard schedule).

2. *Jaundice:* this is an uncommon complication and calls for discontinuance of intensive therapy. No instance of acute yellow atrophy has occurred although Rattner and Falk (1942) observed a case of severe hepatitis with other visceral damage (see below). For the treatment of this reaction, the patient may be given intravenous 10% dextrose solution, high carbohydrate-low fat diet, and injections of liver extract therapeutically. Intestinal elimination should be encouraged with saline catharsis.

3. *Blood dyscrasias* (especially purpura or bleeding from any part of the body): rarely encountered, but necessitating permanent discontinuance of all arsenotherapy. Treatment usually consists in blood transfusions.

4. *Exfoliative dermatitis:* rarely, if ever, encountered. Requires permanent discontinuance of all arsenotherapy. Symptomatic treatment, dextrose intravenously, and liver extract.

5. *Encephalopathy:* women are especially susceptible. This reaction may be manifested by severe headache, vertigo, tremor, fever, unusually severe nausea and vomiting, mental confusion, disorientation, and apathy; by single or repeated convulsive seizures, and by prolonged chorea. In serious instances hyperthermia usually supervenes and *death* may result. May occur on the 3th to 5th day of treatment, or not until the 6th or 7th day; rarely thereafter. Often preceded by headache of increasing severity (see above). There is no means of anticipating this reaction (Thomas, Wexler and Dattner, 1942). In mild cases, the suspicion of toxic encephalopathy should be checked by examination of the spinal fluid for cells, globulin or increased protein. If such tests are positive, further treatment with arsenical drugs should be abandoned. If the spinal fluid is normal, treatment may be resumed if the symptoms have completely disappeared and the temperature is normal.

Treatment of this serious reaction is of uncertain value but the prognosis is not as bad as is usually assumed (Chargin, 1940). Suggested procedures include (1) repeated drainage of spinal fluid (20 to 40 cc.) in repeated taps daily; (2) dehydration by use of intravenous 50% sucrose solution, 50 to 200 cc.; (3) sedation is of value in all cases. Where symptoms are mild, any of the barbiturates may be used by mouth. If convulsions occur, sodium amytal 0.24 gm. ($3\frac{3}{4}$ gr.) may be given intravenously or intramuscularly (this dose may be repeated every 2 to 3 hours for several doses if convulsions occur or the patient is restless; (4) adrenalin. Oxygen inhalations may also be given. Sodium thiosulfate is of no value (Chargin, 1940).

6. *Severe renal injury* (rare); Thomas and his colleagues (1943) have reported acute nephrosis in patients receiving short arsenical and prolonged fever treatment but no particular renal damage occurs in their patients treated with the multiple injection method (10- or 6-day). Rattner and Falk (1942) reported a severe case with acute glomerulonephritis, anuria, uremia, hepatitis, ileus and pericarditis in a patient treated by the 5-day method. This is *rare*.

Post-treatment Routine After 5 to 10 Day Intensive Therapy (to be carried out before discharge from hospital). (1) Complete physical examination. (2) Laboratory studies. (*a*) Titered blood serologic test for syphilis. (*b*) Complete urine analysis. (*c*) Complete blood count (hemoglobin, red blood cell and white blood cell count and differential). (*d*) Other laboratory procedures (icterus index, serum bilirubin, urobilinogen, non-protein nitrogen where indicated).

Outline of Proposed 12-Week Schedule of Modified Intensive Treatment (Eagle, 1943). Patients are to be treated with mapharsen (arsenoxide) 3 times weekly (Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday) at the following dosage scale: less than 120 pounds (55 kg.), 50 mg.; 120 to 155 pounds (55 to 70 kg.), 60 mg.; greater than 155 pounds, 70 mg. Treatment is to continue for 12 weeks or to a total of 36 injections. Hospitalization is not necessary, and patients are to be treated on "duty status." Patients are to receive intramuscular injections of bismuth

subsalicylate (0.2 gm., equivalent to 0.13 gm. of metallic bismuth) once weekly throughout the course of mapharsen (arsenoxide) treatment, to a total of 12 injections.

Follow-up Observation After All Methods of Intensive Chemotherapy. 1. Patient should be reëxamined at monthly intervals for 6 months.

2. This reëxamination should include a complete physical examination with special attention to the mucous membranes of the mouth and throat, the genitals and the perianal region for easily overlooked evidences of infectious relapse.

3. Quantitative blood serologic tests for syphilis should be performed monthly for 6 months, and then at the 9th and 12th month. (The blood serologic reactions usually become negative at the 12th to 16th week after the start of treatment).

4. Examination of the spinal fluid should be done, if feasible, sometime between the 6th and 12th month.

5. The patient should not receive any further anti-syphilitic therapy, except as specifically set forth under "management of the unsatisfactory case."

Management of the Unsatisfactory Case. A patient who has become clinically "cured" and serologically negative and remained so until the 12th month of observation, and in whom the spinal fluid is negative, may be discharged from observation as a "satisfactory result." Should such a person return at a later date with a new dark-field positive lesion, this may be considered as a new infection and the patient may be re-treated in the original manner (Schoch, 1943; Moore, 1943; L. W. Shaffer, 1943). A case must be considered as unsatisfactory or a treatment failure, if: (*a*) There is definite objective evidence of infectious relapse, corroborated by a positive blood serologic reaction for syphilis, and if possible by positive dark-field examination. (*b*) There is incontrovertible evidence of serologic relapse without clinical relapse, *i. e.*, the patient's blood serologic reaction has dropped to negative or near negative and then to persistently strongly positive (this is best interpreted by a quantitative procedure). (*c*) Reagin fastness, *i. e.*, where the blood serologic reaction for syphilis has never reverted to negative but remains persistently positive (preferably determined by a constant titer of quantitative tests) for a 6 months period after treatment.

The unsatisfactory case (infectious relapse, serologic relapse, seroresistance, and the new infection) may be re-treated by intensive therapy except in the event of serious reaction from the original treatment. The results of intensive re-treatment of the unsatisfactory case have not been fully evaluated, but appear to be less satisfactory than original treatment.

Special Considerations Concerning Early Syphilis Treatment. *Criteria of Adequacy of Treatment for Syphilis.* The answer to this question depends fundamentally upon the definition of "adequacy." If by adequacy is meant the securing of a condition of non-infectiousness in an infectious case, one kind of answer will be appropriate; if adequacy is to be interpreted in terms of clinical or of radical cure, another answer will be appropriate; if adequacy means the placing of an infected individual at one or another type or stage of involvement in syphilis on asymptomatic status that will permit of full or limited service in the armed forces, still another answer is necessary. The subject is dealt with under each of these three heads briefly as follows:

Treatment of Non-infectiousness. The immediate infectiousness of surface lesions of syphilis is controlled in all but the rare treatment-resistant or arsenic-fast case, it will be recalled, by the first one, or at most two, injections of an effective trivalent arsenical, provided the dose is adequate (0.3 to 0.5 gm. arsphenamine 606; 0.4 to 0.6 gm. neoarsphenamine; 40 to 60 mg. mapharsen). The duration of this effect of 1 or 2 injections is not precisely known, but is estimated roughly as approximately 30 to 90 days. Failure to continue treatment does not necessarily, but may in a percentage of cases ranging from 0% to 64%, lead to infectious relapse.

A useful tabulation from the Cooperative Clinical Group and the University of Pennsylvania material is herewith presented:

Arsenical treatment alone, number of injections	Infectious relapse (%)	Additional heavy metal injections	Infectious relapse (%)
1– 4	64	20†	45.0
5– 9	14	20	9.0
10–19	..	20	4.0
20–29	..	20	3.6
28.8*	..	28.2 or more	0
30–40		"appropriate"	1.2

From this tabulation it will be apparent that the critical point at which sharp reduction in the probability of recurrent infectiousness takes place is between the 5th and 9th injections of the arsenical (14% relapse without and 9% with heavy metal); and that the so-called 20–20 standard, often quoted as adequate for treatment to non-infectiousness, reduces the risk of infectious relapse to 4%, beyond which a slow reduction to 0% to 1.2% is secured by prolonging treatment beyond 20 arsenical injections with 30 or more injections of heavy metal.

Heavy metal, in the statistical table presented above, is taken to represent 0.2 gm. of an insoluble bismuth salt of not less than 57% metallic content, or 1 week of mercurial inunctions, or its intramuscular equivalent in a water-soluble or insoluble mercurial salt.

It will presently be apparent therefore that the best treatment to secure non-infectiousness is practically identical with the optimum treatment for the securing of "satisfactory results" or "cure."

The Influence of the Development of Secondaries on Relapse. An interesting and seemingly paradoxical situation was revealed in the comparison of serological with clinical relapse under treatment—a relation of particular importance because it might well form the basis for polemic discussion. The stage of syphilis at which treatment is begun influences the incidence of mucocutaneous relapse in a different way from that in which it affects all other forms of relapse. The first Cooperative Clinical Group survey of mucocutaneous relapse as such[44] indicated that it occurs in 10% of patients beginning treatment in the seronegative primary stage; 8.6% of those beginning treatment in the seropositive primary stage; and only 4.2% in those who began treatment after their secondaries had fully developed.‡ Relapse incidence of the mucocutaneous type was therefore markedly less if the patient was allowed to develop his full cutaneous secondary reaction to the disease, the difference amounting to as much as 58% reduction in probability as the patient passed from a seronegative primary to the florid secondary phase. On the other hand, the existence of a distinct relapsing type was foreshadowed by the fact that patients who began treatment with late or recurrent secondaries relapsed in 22.3% of cases. Serologic relapse, on the other hand, occurred in 12% of patients whose treatment was begun in seronegative primary syphilis; 15.1% under the same circumstances in early secondary syphilis (1st year); and 20% if treatment was not begun until delayed secondaries after the 1st year. It appears, therefore, that to begin the treatment of a patient in the sero-

* University of Pennsylvania figures; all others are C. C. G.

† One week of mercurial inunctions equals 1 injection.

‡ The percentages estimated on the basis of 3244 cases observed and treated for six months or over were seronegative primary 16.4%, seropositive primary 20.2%, secondary (first year) 9.5%, secondary delayed 9.2%. The principle illustrated is the same in both.

negative stage of primary syphilis, while it has already been shown definitely to increase the prospect of complete cure, nonetheless subjects him to a definite slight risk of mucocutaneous recurrence and therefore of more prolonged infectiousness. The probable explanation, of course, is that the skin and mucous membranes have never been given the opportunity to develop what might be thought of as a local tissue immunity by full reaction to the disease.

It must, of course, be appreciated that the reduced incidence of relapse and progression in patients who have had secondaries arises simply from the fact that in reaching that stage they have automatically, so to speak, set behind them that much of the life history of the disease. It must, too, remain for further study to decide whether the increased risk of infectious recurrence after early treatment justifies postponement until the patient has developed secondaries. At the present time the higher proportion of curative results seems to justify immediate treatment rather than postponement. The increased risk of infectiousness through recurrence can hardly be greater than the risk of infectiousness represented by a patient who is allowed to live at large in the community without benefit of the arsphenamines until his secondary eruption has fully developed. In any event, the application of such a principle demands universal hospitalization for the patient between the primary stage and the full development of secondaries, an obvious impracticability at this time. Until the proponents of postponement (as for example, Bernard) can advance indubitable evidence that there is other than merely mucocutaneous protective value in permitting a patient to go on to secondaries, the postponement of treatment until secondaries develop is not only against the interests of the public health but against that of the individual patient who above all things, desires the greatest possibility of personal cure.

Jadassohn, from an international questionnaire,[24] has reported that the effect of arsphenamine in controlling the infectiousness of syphilis had led to an estimated reduction in incidence of new cases of the disease of 75% to 80% in Belgium, Sweden, and Holland; 60% in Finland; 50% in Denmark; 50% to 80% in Switzerland; 30% to 60% in Italy and Czechoslovakia; and 25% in Norway.

Rules for Preventing Infectious Relapse. The prevention of infectious recurrence and the reduction of relapse to the lowest possible terms requires of the practitioner, then, an unhesitating acceptance of the following rules: (1) The concept of abortive cure by short courses should be abandoned, no matter how early the patient may come under treatment. (2) Not less than 20 injections of an arsphenamine, and more if possible, preferably in 1 or 2 courses, and an equivalent amount of heavy metal without rest intervals, should be given in an early case to control infectiousness. (3) Treatment should be continuous rather than intermittent or intensive, there being no time, at least within the first year or more, that the patient is not under the influence of one or another effective mode of treatment for syphilis with an arsphenamine or heavy metal. (4) Treatment should be massed well to the fore—that is, within the first 3 months, for this is the period in which mass as distinguished from prolongation, reaches its greatest effectiveness in preventing relapse. (*Cf.* Massive dose arsenotherapy.)

Stokes, Miller and Beerman[45] in their study of bismuth arsphenamine sulfonate observed a similar phenomenon. The proportion of relapse in continuous treated cases was 9.1% and in those allowed rest intervals 14.3%. Of the continuously treated cases 60% had comparatively little treatment (20 injections or less) while

86% of the intermittently treated patients who had the higher incidence of relapse had had comparatively heavy courses of 21 injections or more (40% had over 40 injections). It appeared that a small amount of treatment continuously applied yielded fewer relapses of all kinds than a larger amount with rest periods or lapses.

With so much emphasis placed on the seriousness of lapse in the promotion of infectious recurrence, it is proper to emphasize as the 5th rule for the physician, his responsibility in educating his patient and in holding him to a sufficiently prolonged course and in utilizing follow-up assistance if and when it is available. (6) He should understand, too, that infectious relapse is detected by actual physical examination with special emphasis on the mouth, anus, and genitalia rather than by serologic tests. One should examine especially the lips, penis, scrotum and vulva. (7) Positive serologic tests may warn of infectious relapse and confirm the diagnosis, but since they cannot be frequently applied, physical examination and instruction of the patient himself in the recognition of infectious lesions are the more important approaches. (8) Serologic tests and stripped physical examinations, to be of value in detecting relapse, should, if anything, be more frequently made after treatment is completed and the patient is put on observation than during treatment itself. The opposite is common practice, and this applies especially to the first 2 or 3 years of the disease. (9) Negative serologic reactions, as has been repeatedly emphasized, are not proof of non-infectiousness, immediate or future. A negative serologic reaction should not deceive the physician or patient into relaxing precautions. (10) Treatment and time are the chief preventives of infectiousness. (11) Since potentially infectious relapses occur overwhelmingly in the first 2 years of early syphilis, sexual relations and intimate contact without absolute protection should be allowed *only while the patient is under actual arsenical treatment.* The duration of non-infectiousness when treatment is stopped before the 12th injection of arsphenamine may not, apparently, exceed 1 month.

Adequacy With Respect to "Cure" or "Satisfactory Results." Information on this subject is based on case material observed for not less than 2, and upward to 20, years since the onset of the infection or the institution of treatment. Material of less than 2 years of observational control is fundamentally weak in its demonstration of the possibility of relapse, since the first 2 years of infection are overwhelmingly those of relapse predisposition. On adequacy in the sense of "satisfactory results," 5 groups of data will be quoted: (*a*) Cooperative Clinical Group results in the treatment of early syphilis by a continuous alternating use of arsenical and heavy metal without rest period, through 65 weeks of treatment observation; (*b*) Padget's[36] Johns Hopkins Hospital Syphilis Clinic report on 551 patients completely reëxamined 5 years or more after the termination of their original treatment for early syphilis; (*c*) optimal treatment for early syphilis, 1 to 20 years observation;[12] (*d*) a shortened 20-week system, Hood[23] reporting on Johns Hopkins Hospital material; (*e*) the 5-day intensive intravenous drip arsenotherapy of syphilis (without the use of heavy metal), Leifer, Chargin and Hyman (1941) and Elliott, Baehr, Shaffer, Usher and Lough (1941).[16]

It is not possible at this time to offer more than speculative estimates on 10-day multiple syringe and 10- to 12-week intensive mapharsenbismuth[16] systems which are under study.

The Cooperative Clinical Group's standard treatment system experience indicates that for satisfactory results, treatment must be continuous and not inter-

mittent or irregular, and must combine the alternate use of an effective arsenical (mapharsen is not represented in this material) and a bismuth. Striking reductions in effectiveness with occurrence of infectious relapse, progression of syphilitic manifestations, serologic relapse and seroresistance occur in all phases of early syphilis in which intermittence or irregularity is allowed to occur. Disregarding the precise system of administration, the highest proportion of satisfactory results in seronegative primary syphilis was obtained with 10 to 19 injections of arsphenamine with accompanying heavy metal; in seropositive primary syphilis, with 25 to 35 injections; in early secondary syphilis (seen in the 1st year) 20 to 29 injections. Higher rather than lower dosage of the arsphenamine is recommended. Failure to secure a satisfactory result by 20 injections or less may be met by 10 additional injections, plus heavy metal, which may double the proportion of unsatisfactory outcomes reclaimed. The irreducible margin of failure in the treatment of early syphilis by older standards ranges from 4% to 27%, depending on method, stage at which treatment is begun, adequacy of treatment during the first 2 years of infection.

The Johns Hopkins Syphilis Clinic material[36] is particularly valuable because of the length of observation (over 10 years in half of the patients), and shows clearly the importance to adequacy of the treatment results of the stage at which treatment is begun (82% cure in seronegative primary syphilis, 68.8% in secondary syphilis, 58.7% in early latent syphilis). The poorest results, as in the Cooperative Clinical Group series were observed among patients whose treatment was begun in the seropositive primary stage. Cure was obtained by 83.4% of the patients whose treatment during the first 6 months was by a continuous system, and is increased to 90.4% if treatment during the next 6 months was likewise continuous. It was shown that the final or "adequate outcome" depended in a directly quantitative fashion not only on the number of doses of the arsphenamine received, but also inversely, upon the time span during which it was given. In other words, the more injections in the shorter time, the better the results. The development of early or intermediate relapse was found to be of grave prognostic significance.

Cannon found in a series of some 600 patients treated with 3 standard arsphenamines, that arsphenamine 606 was incontestably superior to neoarsphenamine or silver arsphenamine, and that 1 year of regular and continuous treatment with the arsenical injections closely spaced (2- and 3-day intervals in the first 3 to 5 weeks and at intervals of not less than 1 week thereafter) gave the highest proportion of satisfactory results. The difference between seronegative primary, seropositive primary and secondary syphilis was not more than 6%.

The 20-20 Arsenical-Bismuth Simultaneous Injection Course (Hood). This shortened system, not comparable because of longer intervals (weekly) with the 26-week system of Circular Letter No. 74, utilizes weekly injections of mapharsen and simultaneous weekly intramuscular injections of an oil-suspended bismuth salt. The maximum period of observation (33 months) was only sufficient to indicate that the proportion of unsatisfactory results in the form of seroresistance, serorelapse, clinical relapse and involvement of the central nervous system, amounting to 13.6% of the observed series, was approximately that of unsatisfactory results obtained in early syphilis treated with other arsenical drugs and treatment systems. If confirmed by longer observation, such a treatment system should show how little rather than how much treatment is necessary to produce the average or so-called "standard" results which are so strikingly uniform throughout the entire range from 5-day intravenous drip to 65-week continuous combined therapy.

Massive Dose Arsenotherapy ("5-Day Drip"). The 2 series, Leifer *et al.*, and Elliott *et al.*, the former with of course the longer series of observed cases, illustrates the following principles regarding adequacy: (*a*) Curative results can be obtained with a trivalent arsenical alone (neoarsphenamine, mapharsen). (*b*) Of the two, mapharsen because of its low reactivity is the drug of choice, and 1200 mg. administered in 5 days, the optimum dose. (*c*) In seronegative primary syphilis, 90 to 100% pursue a satisfactory and uneventful course; without reference to type of drug or stage of disease, an aggregate of 81% secured a satisfactory result in one 5-day course, and one re-treatment in 15 cases raised the result to approximately

88% for the entire series (Leifer *et al.*). Elliott and co-workers estimated their curative results at at least 85% of all cases with early syphilis.

Adequacy of Treatment From the Standpoint of Service in the Armed Forces. A tentative basis for evaluation proposed for admission of registrants with syphilis to the United States Army is as follows:

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease; or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for unlimited military service: (*a*) Provided that a negative spinal fluid since treatment was begun has been reported from a trustworthy source; and (*b*) provided that in infections estimated to be of less than 4 years duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent with a minimum total of 75 injections have been given, with approximate continuity (no rest periods or lapses) during the first 30 weeks of treatment; and (*c*) provided that except as further qualified below in infections estimated to be over 4 years duration, at least 20 arsenical injections or its equivalent with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 8 weeks, being allowable.

Evidence of duration of the infection shall be weighed by the examiner with due regard for the age, general venereal history and medical guidance of the registrant.

In infections of *unknown duration* it shall be presumed for classification purposes that those of registrants under 26 years of age are of less than 4 years duration, and over 26 years of age, of more than 4 years duration.

In congenital infections and in acquired infections of more than 10 years known duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid has been recorded at some time after treatment was begun and negative physical examination is recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent," and the registrant eligible for unlimited military service; provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

The Prognostic Significance of Secondary and Serologic Relapse. The following principles, based in the main upon the groups of material cited in connection with the criteria of adequacy of treatment for syphilis, are widely accepted. Early evidence of potentially unfavorable or relapsing course in an early syphilitic infection can be found in (*a*) failure of the primary or secondary lesions to heal under an arsenical therapy; (*b*) continued presence of *Sp. pallida* in the lesions after the employment of a known effective trivalent arsenical (these 2 groups constitute treatment resistance in syphilis;[26] (*c*) prematurely early reversal of a positive serologic reaction on the blood to negative (4th to 7th week in seropositive primary or secondary syphilis); (*d*) failure of a positive serologic reaction on the blood to reverse to negative after the 16th week (in the intensive or 5-day drip system reversal is ordinarily expected by quantitative tests between the 10th and 18th weeks after the institution of treatment but late secondaries may not reverse for many months even though "cured").

Cooperative Clinical Group results[13] (observation period too short) showed a relapse expectancy of 19.7% including all forms, of which, when observed for more than 6 months, 12.1% was mucocutaneous, 3.4% asymptomatic neurosyphilis, 4.1% symptomatic neurosyphilis, and 0.9% cardiovascular syphilis.

The unfavorable prognostic significance of early and intermediate relapse was well brought out in Padget's series in which "cure" was achieved in 73.2% of 456 patients in whom no relapse was observed, whereas only 28.2% of those sustaining an intermediate relapse achieved "cure". Persistent seropositive reactions on the blood, however, occurred in 16% of those who sustained no relapse, and in 10.3% of those who underwent intermediate relapse. Late benign syphilis developed 8 times as frequently in relapsers as in non-relapsers, cardiovascular syphilis

3.5 times as frequently; neurosyphilis 6 times as frequently; multiple late manifestations 7.5 times as frequently in relapsers as in non-relapsers. The occurrence of weak positive serologic reactions on the blood appearing in the course of a series of negatives in treated early syphilis have been emphasized as of relapse significance by certain authors.

Significance of Seropositivity After Treatment Which Was Begun During Early Syphilis. Broadly speaking, Padget's experience indicated that a residue of 14.9% persistent serologic positiveness would appear in a series of early syphilitics on whom the satisfactory results he described had been secured. In these cases there would be no manifestations such as abnormal spinal fluid, cardiovascular disease, visceral disease and so forth to accompany the persistent seropositiveness. The inclination would be, therefore, to rate it in these cases as without significance. In general, however, persistence of a positive serologic reaction on the blood of early syphilitics under treatment by the older standard continuous systems was an indication of presence of asymptomatic neurosyphilis, and called for an examination of the spinal fluid immediately.[25,48] The more intensive foreshortened treatment systems seem so materially to have reduced the likelihood of the occurrence of asymptomatic neurosyphilis that the neurosyphilitic significance of persistent seropositivity will probably be greatly reduced by their use. In addition, to asymptomatic neurosyphilis, syphilis of the cardiovascular system, often coming to recognition 5 or more years after the cessation of treatment, may be included in the prognostic significance of seropositiveness of a persistent type in early syphilis.

The Prevention of Cardiovascular Syphilis. This is still the *terra incognita* of modern syphilology and the studies thus far summarized have thrown relatively little light upon it. Langer[26] and others have attributed the increase in the incidence of aortitis since 1912 to the use of arsphenamine in the treatment of syphilis, but our experience with this drug in early syphilis fails to substantiate this belief, the incidence of recognizable aortic lesions not increasing materially in the period studied. It is, of course, true that our study does not extend forward into the period of maximum recognition of this form of syphilis. Moore, Danglade and Reisinger[29] in considering Langer's contention, believed that the apparent increase coincident with the use of arsphenamine in treatment is due rather to more accurate pathologic study with increasing knowledge of microscopic appearance of aortic syphilis. Progression of cardiovascular syphilis in spite of various methods of treatment occurred in 0.8% to 1.2% of our patients. Warthin's[49] observation, which placed the incidence of aortic syphilis in syphilitic adults between 1909 and 1919 at 97.6%, and between 1919 and 1929 at 86.3%, further supports the view that arsphenamine is not responsible for the apparently increasing incidence observed by Langer.

Moore and Padget[32] in their analysis of seroresistant syphilis (early) emphasize the seriousness of seroresistance in early syphilis and its relatively lesser significance in late syphilis. Twenty-three per cent of their seroresistant group sustained infectious relapse as against 5% who secured prompt serologic reversal. Neurosyphilis occurs in 31% of the seroresistant cases, but in only 18% of those who sustain prompt reversal.

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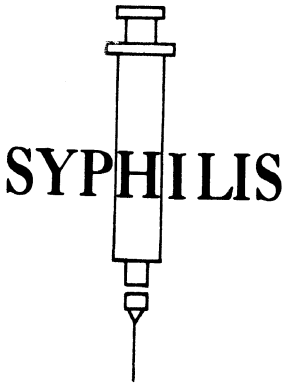

THE TREATMENT OF EARLY SYPHILIS WITH PENICILLIN

A PRELIMINARY REPORT OF 1,418 CASES

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In December 1943 Mahoney, Arnold and Harris [1] reported briefly on the effect of pencillin in experimental syphilis of rabbits and in 4 human patients with seropositive primary syphilis. As a result of these observations and of further experimental studies carried out in the laboratories of Mahoney [2] and Eagle [3] there was organized, about Sept. 1, 1943, under the general auspices of the Committee on Medical Research of the Office of Scientific Research and Development and under the specific direction of the Subcommittee on Venereal Diseases, National Research Council, a cooperative study of the effect of penicillin in syphilis in human beings. A Penicillin Panel was appointed by this subcommittee, with membership including the authors of this paper.[4] Because of the special problems confronting the armed forces, particular emphasis has been laid on early syphilis and on neurosyphilis, though other forms of late syphilis have also been studied. The preliminary results obtained to date are here presented in two papers, this dealing with early syphilis; the other, with Stokes as spokesman for the group, with late syphilis.

The penicillin employed has been derived from Army, Navy, Public Health Service, and Office of Scientific Research and Development sources. Only the sodium salt has been employed in these studies. Penicillin allocated to the Office of Scientific Research and Development for research purposes has been distributed by the Committee on Chemotherapeutic and Other Agents, National Research Council, Dr. Chester Keefer, chairman. This committee has allocated gradually increasing amounts of the drug to the Subcommittee on Venereal Diseases, which in turn has apportioned it among those civilian clinics selected for participation in the study.

Early syphilis is at present under investigation in twenty-three clinics or research centers. These, with the names of the responsible investigators, are as follows: U. S. Army (Fort Bragg, North Carolina, Capt. William Leifer, Camp Howze, Texas, Major Franklin Grauer), U. S. Navy (Naval Medical Center, Bethesda, Md., Lieut. Comdr. E. C. Barksdale), United

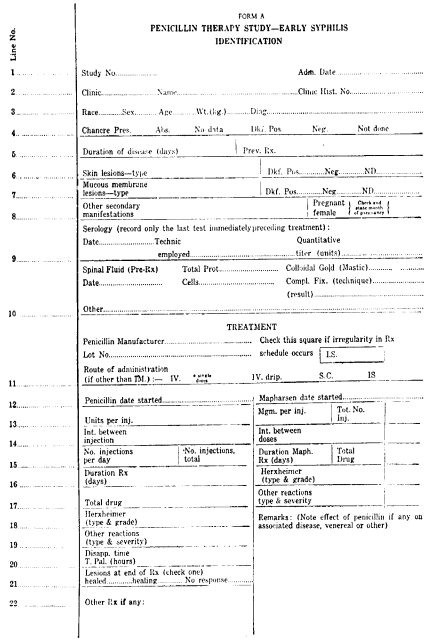
The authors are members of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council.

The work described in this paper was done under several contracts recommended by the Committee on Medical Research of the Office of Scientific Research and Development.

Read in a panel discussion on "Penicillin in the Treatment of Syphilis" before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Mahoney, J. F.; Arnold, D. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**: 355, 1943.
2. Mahoney, J. F., and others: Unpublished data.
3. Eagle, H.: Unpublished data.
4. Dr. J. R. Heller Jr., medical director in charge Venereal Disease Division, United States Public Health Service, was later added to the membership of the panel.

States Public Health Service (Marine Hospital, Stapleton, S. I., Dr. J. F. Mahoney), Massachusetts Memorial Hospital, Boston (Dr. Oscar Cox), Bellevue Hospital, New York (Dr. Evan Thomas), Chicago Intensive Treatment Center (Dr. S. W. Becker), Cleveland City Hospital and University Hospitals (Dr. Harold Cole), University of Pennsylvania Hospital (Dr. J. H. Stokes), University of Texas (Dr. Chester Frazier), Washington University, St. Louis (Dr. W. Barry Wood Jr.), Yale University (Dr. Francis Blake), Dallas Venereal Disease Clinic (Dr. Arthur Schoch), Leland Stanford Jr. University Hospital (Dr. C. W. Barnett), Duke University Hospital (Dr. C. L. Calloway), Vanderbilt University Hospital (Dr. R. H. Kampmeier), Johns Hopkins Hospital (Drs. J. E.



FORM A

PENICILLIN THERAPY STUDY—EARLY SYPHILIS

IDENTIFICATION

Line No.

1 Study No. ..... Adm. Date .....

2 Clinic ..... Name ..... Clinic Hist. No. .....

3 Race ..... Sex ..... Age ..... Wt.(lbs.) ..... Drug .....

4 Chancre Pres. ..... Abs. ..... No data ..... Dk. Fld. Pos. ..... Neg. ..... Not done .....

5 Duration of disease (days) ..... Prev. Rx .....

6 Skin lesions—type ..... Dkf. Pos. ..... Neg. ..... ND .....

7 Mucous membrane lesions—type ..... Dkf. Pos. ..... Neg. ..... ND .....

8 Other secondary manifestations ..... Pregnant female ..... Check test if positive

Serology (record only the last test immediately preceding treatment):

Date ..... Technic ..... Quantitative

9 employed ..... titer (units) .....

Spinal Fluid (Pre-Rx) Total Prot. .....

Date ..... Cells .....

10 Other .....

TREATMENT

Penicillin Manufacturer ..... Check this square if irregularity in Rx schedule occurs LS.

Lot No. .....

Route of administration (if other than IM.):— IV. * orally drug IV. drip. S.C. IS

11 Penicillin date started .....

12 Units per inj. .....

13 Inf. between injection .....

14 No. injections per day ..... No. injections, total .....

15 Duration Rx (days) .....

16 Total drug .....

17 Herxheimer (type & grade) .....

18 Other reactions (type & severity) .....

19 Dicamp. time T. Pal. (hours) .....

20 Lesions at end of Rx (check one) healed ..... healing ..... No response .....

21 Other Rx if any: .....

22

Mapharsen date started .....

Mgm. per inj. ..... Tot. No. Inj. .....

Int. between doses .....

Duration Maph. Rx (days) ..... Total Drug .....

Herxheimer (type & grade) .....

Other reactions type & severity .....

Remarks: (Note effect of penicillin if any on associated disease, venereal or other)

Fig. 1.—Obverse of form for reporting early syphilis by participating clinics.

Moore and C. F. Mohr), Tulane University (Dr. R. V. Platou), Presbyterian Hospital, New York (Dr. A. B. Cannon), University of Virginia Hospital (Dr. D. C. Smith), New York Hospital (Dr. Walsh McDermott) and the Detroit Health Department (Dr. Loren Shaffer). This report is based on the work of these investigators and of many of their associates and assistants, too numerous to name.[5]

These clinics and centers agreed (1) to treat patients with early syphilis on assigned treatment schedules in an effort to define as promptly as possible the all important time-dose relationship and (2) to pool their results under the Penicillin Panel of the Subcommittee on Venereal Diseases. Only those patients in whom the diagnosis of early syphilis was indubitable, on the basis of actual demonstration of treponemes, were to be acceptable. All patients were to be originally examined and subsequently followed in as nearly as possible a uniform manner. The immediate results of treatment were to be reported to the Penicillin Panel on specially devised forms (figs. 1 and 2), susceptible of coding, punch carding and machine statistical analysis.

5. The statistical data have been prepared by Miss Gwendolyn Futcher.

TABLE 1.—*Four Treatment Schedules*

Duration of Treatment	Interval Between Injections	Route of Administration	Single Dose	No. of Injections	Total Dose
7½ days	3 hours	Intramuscular	1,000 units	60	60,000 units
7½ days	3 hours	Intramuscular	5,000 units	60	300,000 units
7½ days	3 hours	Intramuscular	10,000 units	60	600,000 units
7½ days	3 hours	Intramuscular	20,000 units	60	1,200,000 units

On the basis of the very preliminary studies of Mahoney and his associates, there appeared to be five variables requiring study. These were (1) the route of administration, originally chosen [1] as intramuscular for the sake of slightly delayed absorption and excretion as compared to the intravenous route; (2) the interval between injections, at first selected [1] as every three hours day and night on the basis of known data as to the rate of absorption and excretion; (3) the duration of treatment, originally arbitrarily selected as eight days; [1] (4) the total dosage, again arbitrarily selected as 1,200,000 units,[1] and (5) possible combinations of penicillin with other drugs, e. g. mapharsen.

At the outset it was decided by the Penicillin Panel to hold the first three of these variables constant; i. e., all cases were to be treated by the intramuscular route every three hours day and night to a total of sixty injections given in seven and one-half days. The first effort was to be to define the minimum effective dose so given within this time period. Four treatment schedules were accordingly drawn up (table 1).

These covered a twenty fold dosage range up to and including the original maximum arbitrarily chosen by Mahoney and his co-workers. In addition there were originally planned (but subsequently temporarily dropped) two other groups, to test the combined effect of penicillin plus mapharsen. These two groups comprised a total penicillin dosage of 60,000 and 300,000 units respectively plus a total of 320 mg. of mapharsen given in eight divided doses of 40 mg. each daily for eight days. This mapharsen dosage was deliberately selected as a relatively safe and known subcurative dose from which a high rate of relapse might be expected.

Later, as material accumulated, the variable of time was brought under study, and three additional treatment groups were established with a total dosage of penicillin of 300,000, 600,000 and 1,200,000 units respectively given in thirty intramuscular injections every three hours day and night over a four day period. The latter groups have been so recently started as not

TABLE 2.—*Duration of Follow-Up from Start of Treatment in 1,418 Patients with Early Syphilis (June 1, 1944)*

Duration of Follow-Up, Weeks	No. of Patients Followed
1 to 4	671
5 to 8	307
9 to 16	327
17 to 24	107
25 to 48	6

to justify consideration in this paper, which is devoted entirely to the eight day treatment schedule. The only exception to the statement lies in 25 cases treated by the intravenous route before the present organized study began; in them the dosage was variable and the duration of treatment four to eight days.

For the purposes of this report, the books of the Penicillin Panel have been temporarily closed as of May 25, 1944. To that date there had been received 1,587 case reports of early syphilis, of which 1,418 were suitable for analysis as to various points. Of these 177 had seronegative primary, 379 seropositive primary, 698 uncomplicated and 67 complicated [6] early secondary syphilis and 97 various types of recurrent (usually previously treated) secondary syphilis. Of the patients 461 were white, 950 Negro and 7 of other races; 791 were male and 627 female, of whom 58 were pregnant at the time of treatment.

The preliminary nature of this report is indicated by table 2, in which the duration of follow-up after treatment is shown. The majority of patients have so far been observed for less than two months; only 113 of the entire number for four months or longer. This fact must be repeatedly emphasized as a matter of caution; the results here presented are subject to major revision after further observation. It is planned to report further information as it develops at three to six month intervals.

THE IMMEDIATE RESULTS OF TREATMENT

Disappearance Time of Treponema Pallidum from Open Lesions.—Data are available on this point from 663 cases treated with penicillin alone (excluding those cases treated with penicillin plus mapharsen).

Regardless of the single or total dose of penicillin, organisms have promptly disappeared from open lesions in every case within a range of six to sixty hours. At the two extremes of dosage, 1,000 and 40,000 units, the average disappearance time varied only from twenty-one to fourteen hours. Whether the apparent trend toward shortening of disappearance time is significant is open to question because of the varying intervals at which dark field examinations were done in the several clinics. Not shown in the table is the fact that the intravenous holds no advantage over the intramuscular route in this respect.

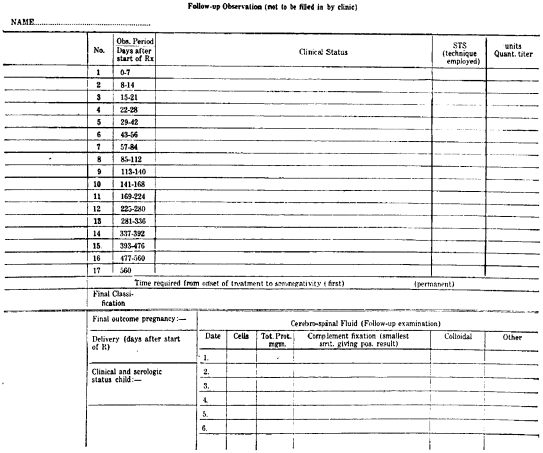
Healing of Lesions.—This is difficult to measure in statistical terms. There has been no observed instance of failure of lesions to heal, regardless of the single or total dose. With a total dosage of 60,000 units in eight days, healing is less prompt than with arsenical therapy; with larger total dosage, 300,000 units and up, it is as rapid as with standard chemotherapy or more so.

Serologic Response.—In figure 3 is shown the median blood serologic response,[7] in terms of quantitative titer, of four groups of patients treated with penicillin alone (excluding those treated with penicillin plus mapharsen). Included are both seropositive primary and secondary syphilis. Regardless of the total dosage, whether 60,000, 300,000, 600,000 or 1,200,000 units, there is apparent a trend toward serologic reversal within a period of about twenty days after the start of treatment. Within the range of 300,000 to 1,200,000 units this trend is approximately uniform, regardless of dosage; with 60,000 units it is a little slower and less pronounced. Parenthetically, this rate of serologic reversal is identical with that observed after arsenical chemotherapy, whether with an arsphenamine at weekly intervals or mapharsen given by various intensive methods.

TABLE 3.—*Average Disappearance Time of Treponema Pallidum from Open Lesions of Early Syphilis After Varying Treatment Schedules (June 1, 1944)*

Size of Individual Dose Given Every Three Hours, Units	Cases	Average Disappearance Time of Treponema Pallidum, Hours
1,000	52	21
5,000	201	20
10,000	237	19
20,000	135	13
40,000	38	14

Further data are shown in tables 4 and 5. In table 4 is summarized the blood serologic response of 48 patients with seronegative primary syphilis observed for nine or more weeks after the start of treatment. These are not broken down by total dosage since, regardless of the range of 60,000 to 1,200,000 units, the response was identical. In 28 patients the serologic test for syphilis, originally negative, remained so throughout the period of observation; in 18 it became temporarily positive, then reverted to negative, and in 2 only there was a subsequent serologic relapse. From the serologic standpoint, therefore, and during the very brief observation period so far available, the results may be said to be satisfactory in 95.8 per cent of the cases.



Follow-up Observation (not to be filled in by clinic)

NAME.....

No.	Obs. Period Days after start of Rx	Clinical Status	STS (technique employed)	units Quant. titer
1	0-7			
2	8-14			
3	15-21			
4	22-28			
5	29-42			
6	43-56			
7	57-84			
8	85-112			
9	113-140			
10	141-168			
11	169-224			
12	225-280			
13	281-336			
14	337-392			
15	393-476			
16	477-560			
17	560			

Time required from onset of treatment to seronegativity (first) (permanent)

Final Classification

Final outcome pregnancy:—

Delivery (days after start of Rx)

Clinical and serologic status child:—

Cerebro-spinal Fluid (Follow-up examination)

Date	Cells	Tot. Prot. mgm.	Complement fixation (smallest amt. giving pos. result)	Colloidal	Other
1.					
2.					
3.					
4.					
5.					
6.					

Fig. 2.—Reverse of form for reporting early syphilis by participating clinics.

TABLE 4.—*Blood Serologic Response in Seronegative Primary Syphilis, Patients Followed More Than Nine Weeks from Start of Treatment, All Treatment Schedules Combined (June 1, 1944)*

	Serologic Test for Syphilis		
Cases Followed	Negative, Remained Negative	Negative, Became Positive, Later Negative	Serologic Relapse
48	28	18	2

6. Complicated by asymptomatic neurosyphilis, syphilitic meningitis or ocular, osseous or visceral lesions.

7. This has been determined by a statistical device which assigns to the initial quantitative titer, regardless of the actual number of units, the numerical value of 100. All subsequent observations are expressed in terms of per cent of the original titer.

In seropositive early syphilis (combining seropositive primary and secondary syphilis) the results, now broken down by treatment schedule, are shown in table 5 (limited to patients observed for nine or more weeks after the start of treatment). Here there is a direct relationship between "satisfactory" and "unsatisfactory" immediate serologic results and total dosage of penicillin; the larger the dose, the better the result. The only and perhaps a major exception to this is in the group of patients who received 300,000 units of penicillin plus 320 mg. of mapharsen in seven and one-half days. This group shows as good initial results as were shown by patients receiving four times as much penicillin without mapharsen.

So far it is clear that the minimum effective dose of penicillin in early syphilis in man cannot be determined on the bases of disappearance time of surface organisms, healing of lesions or (except very roughly) serologic response since, regardless of total dose, within the range employed the drug is effective in all of these respects. The only available criterion lies, therefore, in the incidence of relapse.

TABLE 5.—*Blood Serologic Response in Seropositive Early Syphilis According to Treatment Schedule, Patients Followed More Than Nine Weeks from Start of Treatment (June 1, 1944)*

Treatment Schedule, Units	Cases Followed	Serologic Test for Syphilis Response: Satisfactory (Reversed, or Titer Falling), %	Serologic Test for Syphilis Response: Unsatisfactory (No Significant Change, or Relapse), %
60,000	38	57.8	42.1
60,000 + mapharsen	26	76.9	23.0
300,000	79	82.1	17.7
300,000 + mapharsen	24	91.6	8.3
600,000	109	88.0	12.0
1,200,000	62	90.3	9.6

Relapse After Penicillin Treatment.—In this material, relapse has been rigidly defined. Any subsequent clinical manifestation of the disease, whether obviously relapse or apparently reinfection, has been classified as clinical relapse. Serologic relapse includes not only those who, originally seronegative or rendered so by treatment, subsequently became seropositive but also those who, still seropositive in low titer, subsequently develop high titer tests.[8] An effort has been made to observe all patients clinically and serologically at weekly intervals for the first two months, every two weeks for another two to three months and at least monthly thereafter.

TABLE 6.—*Incidence of Relapse in Seronegative Primary Syphilis Treated by Varying Schedules in Eight Days, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units	Cases Followed	Relapse: Clinical	Relapse: Serologic	Relapse: Total Number	Relapse: %
60,000	1	..	..	..	...
200,000	..	..	..	..	...
300,000	14	1	..	1	7.2
600,000	21	1	1	2	9.5
1,200,000	52	..	..	..	...
Intravenous (see text)	4	..	..	..	...
Total	92	2	1	3	3.2

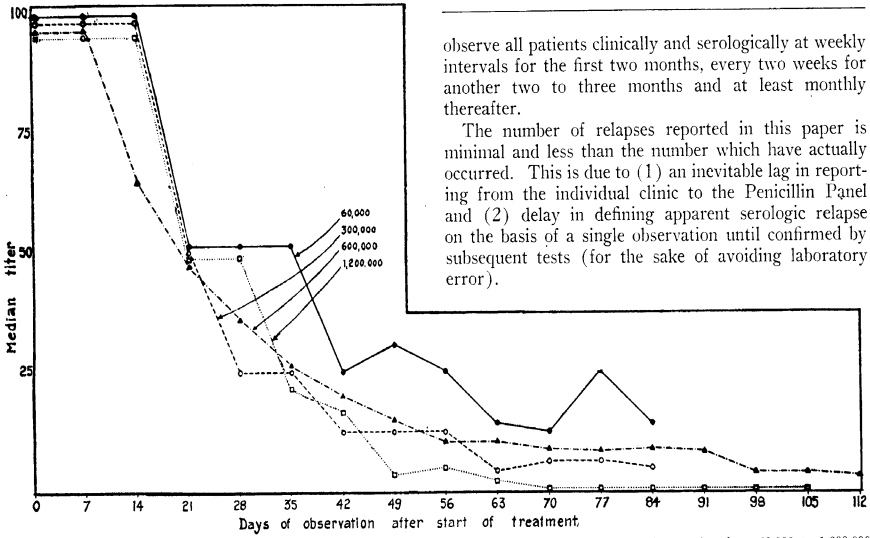


Fig. 3.—Median serologic response of seropositive early syphilis to penicillin with four treatment schedules ranging from 60,000 to 1,200,000 units total dose in eight days; June 1, 1944.

The number of relapses reported in this paper is minimal and less than the number which have actually occurred. This is due to (1) an inevitable lag in reporting from the individual clinic to the Penicillin Panel and (2) delay in defining apparent serologic relapse on the basis of a single observation until confirmed by subsequent tests (for the sake of avoiding laboratory error).

The method of statistical reporting here adopted is recognizedly inaccurate in that the incidence of relapse is related to the total number of patients observed for a period of time greater than that of the earliest observed relapse. In the tables to follow all patients are included who were observed for thirty-eight days or longer after the start of treatment, since this was the shortest interval at which relapse was observed. The brief interval available for study prevents the adoption of the statistical method used by Eagle,[9] which will, however, be utilized in later more definitive analyses. Preliminary rough test of this method of appraisal suggests that the eventual incidence of relapse will probably be from four to five times as great as that reported here. In table 6 is shown the incidence of relapse, clinical and serologic, in 92 patients with sero-

8. Not yet classified as relapse or "unsatisfactory result" are those patients whose serologic tests have shown no improvement. Twelve months after treatment will be allowed to elapse before such patients are classified as seroresistant.

9. Eagle, H.: The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen: A Preliminary Analysis of the First 4,823 Cases, to be published.

negative primary syphilis. The numbers, broken down by treatment schedule, are too small to be significant, though the total observed relapse rate, 3.2 per cent, is low.

Similar data for seropositive primary syphilis are shown in table 7 and for secondary syphilis in table 8.

TABLE 7.—*Incidence of Relapse in Seropositive Primary Syphilis, Treated by Varying Schedules in Eight Days, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	8	2	..	2	25.0
200,000	3	..	..	..	....
300,000	30	2	1	3	10.0
600,000	37	..	..	..	....
1,200,000	75	1	1	2	2.6
Intravenous (see text)	5	1	..	1	20.0
Total*	153	6	2	8	5.0

TABLE 8.—*Incidence of Relapse in Secondary Syphilis Treated by Varying Schedules in Eight Days, Patients Followed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	37	9	2	11	29.6
200,000	8	3	..	2	37.5
300,000	94	6	4	10	10.6
600,000	136	4	3	7	5.0
1,200,000	64	..	2	2	3.1
Intravenous (see text)	16	1	1	2	12.5
Total	355	23	12	35	9.8

These relate to patients treated with penicillin alone (excluding the combined penicillin with mapharsen groups). Here there is obvious a direct correlation between total dose and relapse incidence.

The data of tables 6, 7 and 8 are combined in table 9 for all patients with early syphilis; and here is added information concerning the patients treated with penicillin plus 320 mg. of mapharsen (two groups, 60,000 and 300,000 units respectively) and also concerning a small group of patients (25 in number) treated by the intravenous route before the present organized study was begun. In patients treated with penicillin by the intramuscular route the incidence of relapse, even in the brief observation period available, is in direct proportion to total dosage (nearly 30 per cent with 60,000 units, only 2 per cent with 1,200,000 units). In the small group who received large doses intravenously, ranging from 600,000 to 1,200,000 units, and whether by multiple injections or continuous drip, the observed relapses are five to six times as great as in patients treated with comparable doses by the intramuscular route, suggesting that the intravenous route not only holds no advantage over the intramuscular route but is actually less effective.

In table 10 the incidence of relapse is related to the stage of disease at the start of treatment in patients treated with penicillin alone (omitting the groups combined with mapharsen, among which only 1 relapse has so far occurred) and without regard to total dosage. In conformity with Eagle's report [9] as to semi-intensive arsenotherapy, and in contrast to the older Cooperative Clinical Group and other data [10] as to "standard" prolonged arsenical chemotherapy, there seems to be here a direct relationship between the stage of the disease at the time of starting treatment and the incidence of relapse. The proportions in patients treated with penicillin alone are 3.2 per cent for seronegative primary, 5.0 per cent for seropositive primary and nearly 10 per cent for early secondary syphilis.

Table 11 shows the average and extreme intervals between the start of treatment and observed relapse. Here there is no direct correlation as to total dose. Relapses have occurred as early as thirty-eight days and as late as two hundred and ninety-four days after the start of treatment. Considering the short periods of observation so far available for all groups treated, further relapses in all may be confidently anticipated.

The Optimum Time-Dose Relationship for Penicillin in Early Syphilis.—The available data indicate that within the twentyfold dosage range employed in a period of seven and one-half days penicillin has a profound immediate effect in terms of disappearance of surface organisms, healing of lesions and serologic reversal. In seronegative primary syphilis no statements as to minimum effective dose are as yet justifiable. In seropositive primary and early secondary syphilis any dose less than 600,000 units in seven and one-half days is clearly ineffective. A total dose of 600,000 units provides a minimum relapse rate of nearly 5 per cent, of 1,200,000 units a rate of 2 per cent, within the short period for which such patients have so far been followed. The intravenous route appears to be less effective, even in large doses, than the intramuscular.

The possibility that even 1,200,000 units in a four to eight day period will prove to be inefficacious after further observation has led the Penicillin Panel to inaugurate the study of two additional treatment groups given a total of 2,400,000 units in thirty and sixty intramuscular injections in four and seven and one-half days respectively. These patients are being treated in the United States Army and eight selected United States Public Health Service rapid treatment centers.

The results obtained to date in the two small groups of patients given 60,000 and 300,000 units of penicillin respectively, in each case plus the known subcurative

TABLE 9.—*Incidence of Relapse in All Types of Early Syphilis Treated by Varying Schedules, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units (Route Intramuscular Unless Specified)	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	46	11	2	13	28.2
60,000 + 320 mg. mapharsen	26	..	..	..	....
200,000	11	3	..	3	27.2
300,000	138	9	5	14	10.1
300,000 + 320 mg. mapharsen	68	1	..	1	1.4
600,000	194	5	4	9	4.6
1,200,000	191	1	3	4	2.0
Various intravenous schedules *	25	2	1	3	12.0

* Dosage range 600,000 to 1,200,000 (all but 3 cases 1 million +), single intravenous injections, intravenous drip or both, in 4 to 8 days.

TABLE 10.—*Incidence of Relapse by Stage of Disease, All Treatment Schedules* Combined, Patients Followed More Than Thirty-Eight Days (June 1, 1944)*

Stage of Disease	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
Primary seronegative	92	2	1	3	3.2
Primary seropositive	158	6	2	8	5.0
Secondary	355	23	12	35	9.8

* Omitting 94 patients treated with penicillin + mapharsen.

10. Stokes, J. H., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Early Syphilis, Ven. Dis. Inform. **13:** 165, 207 and 253, 1932.

total dose of 320 mg. of mapharsen in eight days, are worth emphasizing. In 94 such patients followed for thirty-eight days or more only one relapse has occurred. It is perhaps to be expected that certain patients with early syphilis will prove to be resistant to penicillin exactly as a relatively standard proportion of 5 to 15 per cent of patients has proved to be resistant to arsenic heavy metal chemotherapy. But, in view of what is already known concerning the probable modes of action of penicillin and of arsenic and bismuth in syphilis (considerations too lengthy for discussion here) it is possible that those patients resistant to penicillin will not be the same ones resistant to metal chemotherapy and that a combination of the two forms of treatment will eventually prove to be more effective than any method of use of either one alone.

It should also be emphasized that penicillin, as so far employed in early syphilis, is not suitable for mass application. Injections every three hours day and night over whatever period of time demand hospitalization and trained nursing or professional care. However available these may be for the armed forces, facilities are inadequate in civilian practice to meet the enormous demand. The eventual general use of the drug depends on the development of methods which will permit its administration on an ambulatory basis.

TABLE 11.—*Average and Extreme Intervals from Start of Treatment to Relapse According to Treatment Schedule (June 1, 1944)*

Treatment Schedule, Units	Average Interval, Days	Extreme Intervals, Days
60,000	104	64 to 154
60,000 + mapharsen	No relapses observed	
200,000	116	83 to 135
300,000	90	38 to 166
300,000 + mapharsen	..	53*
600,000	98	73 to 113
1,200,000	132	61 to 294
Intravenous	74	56 to 126

* One relapse only.

As with arsenical chemotherapy, it is probable that the optimum time-dose relationship for the treatment of early syphilis in man with penicillin alone and its relative efficacy when administered alone or in combination with other forms of treatment will be guided by data from the experimental laboratory not as yet available but shortly to be expected.

In man, further immediate studies should be directed to (1) determination of the relative effectiveness of 1,200,000 units versus much larger doses in four and eight days respectively, (2) variation of the time interval between individual dosage within the range of three to twenty-four hours, (3) more exact definition of the merits of intravenous versus intramuscular administration and (4) an expansion of the combinations penicillin plus arsenic and penicillin plus bismuth.

Results of Treatment of Special Forms of Early Syphilis.—Thirteen patients with early syphilis in this series had positive spinal fluids before treatment (11 of them group 2, 2 group 3). Of these, the fluid abnormalities disappeared or improved under penicillin treatment alone in 10 within time period ranging from ten to fifty days; 3 were unimproved.

Acute Syphilitic Meningitis.—Ten patients with this complication of early syphilis have been treated, the majority with 1,200,000 units in seven and one-half days. Symptomatic relief has been dramatically prompt in all and, in the majority, spinal fluid abnormalities have disappeared or are rapidly improving.

Treatment Resistant Early Syphilis.—Eight patients, most of them with dark field positive psoriasiform syphilids, persisting in spite of or recurring during metal chemotherapy, have been treated with penicillin, with prompt healing in all and with subsequent serologic behavior similar to that of previously untreated early syphilis.

Infantile Congenital Syphilis.—Not included in the tabular presentations are some 20 infants with early congenital syphilis. The majority of them have been treated with a total dose of penicillin of 20,000 units per kilogram of body weight, corresponding to a total dose of 1,200,000 units in the adult. Their behavior in terms of symptomatic improvement and serologic response is analogous to that of early acquired syphilis in the adult.

The Outcome of Pregnancy.—Though 58 pregnant women with early syphilis have so far been treated, it is too early to speak of any results as to the outcome in the child.

REACTIONS TO PENICILLIN

Herxheimer Reactions.—Of 1,418 patients treated, 846 (59 per cent) have had Herxheimer reactions within the first twenty-four hours. This consists usually of fever alone (685 cases); in the others, exacerbation of secondary skin lesions with or without fever. The fever is usually mild (less than 102 F.), though in 174 cases (12 per cent) the febrile rise has been higher than this level. In no case has the reaction been alarming, nor has it interfered with subsequent treatment.

Other Reactions.—Only 59 patients (41 per cent of the total treated) have had other reactions attributable to penicillin. In 15 there were cutaneous eruptions (8 urticaria, 7 other types of skin rashes, none severe). Seven had mild gastrointestinal reactions, 33 secondary fever, 2 abscessed buttocks and 2 miscellaneous mild disturbances. In no case has penicillin treatment had to be suspended because of reactions from the drug.

SUMMARY

1. An organized study of the effect of penicillin in early syphilis is in progress in an effort to determine the optimum method of use of the drug. The results so far available are preliminary.

2. Penicillin has a profound immediate effect in early syphilis in terms of (*a*) disappearance of surface organisms from open lesions, (*b*) healing of lesions and (*c*) a trend toward serologic reversal.

3. These immediate effects are in general identical within a twentyfold dosage range of 60,000 to 1,200,000 units administered by the intramuscular route every three hours day and night to a total of sixty injections in seven and one-half days.

4. The same immediate effects are apparent within the dosage range of 300,000 to 1,200,000 units given by the intramuscular route every three hours day and night to a total of thirty injections in four days.

5. These immediate effects cannot be utilized to determine the optimum time-dose relationship, which, in man, depends on the incidence of relapse.

6. The incidence of relapse, when penicillin is administered alone, is in direct relationship to the total dosage given by the intramuscular route in a seven and one-half day period, greatest with 60,000 units and least with 1,200,000 units.

7. Relapse appears to be more frequent after intravenous than after intramuscular administration of comparable doses.

8. The lowest incidence of relapse—and the most favorable serologic response—was in small groups of patients treated with 60,000 and 300,000 units respectively of penicillin plus a known subcurative dose of mapharsen.

9. Penicillin has a favorable effect in early asymptomatic neurosyphilis, acute syphilitic meningitis, early syphilis treatment resistant to arsenic and bismuth and infantile congenital syphilis.

10. No opinion can be as yet expressed as to the effect of penicillin in the prevention of prenatal syphilis.

11. The optimum time-dose relationship of penicillin in early syphilis is not yet established. Certainly the minimum dose, especially in secondary syphilis, should not be less than 1,200,000 units; probably it should be more.

12. Herxheimer reactions after the penicillin treatment of early syphilis are frequent but not serious; other reactions, due to penicillin itself, are negligible.

13. Further avenues of study are suggested.

SYPHILIS

PENICILLIN TREATMENT OF SYPHILIS.

1. PURPOSE. The purpose of this bulletin is to introduce penicillin treatment of syphilis in the Army and to outline the administrative and professional details involved. When penicillin is not obtainable through normal supply channels the system of treatment recommended in S. G. O. Circular Letter No. 74, 25 July 1942, subject, "Diagnosis and treatment of the venereal diseases," will be used.

2. INDICATIONS FOR PENICILLIN TREATMENT OF SYPHILIS. Penicillin will be used in the treatment of the following types of syphilis:

a. Untreated primary and secondary syphilis. (Mapharsen-bismuth treatment has not been initiated.)

b. Untreated latent syphilis. (Mapharsen-bismuth treatment has not been initiated.) It is essential that a preliminary spinal fluid examination be made in all cases of presumed latent syphilis. If the spinal fluid is abnormal as defined in paragraph 4*a* (2), TB MED 48, 31 May 1944, the case must be classified as asymptomatic neurosyphilis and be managed according to that directive.

c. Treated primary and secondary syphilis which has failed to respond to mapharsen-bismuth therapy. This includes—

(1) Clinical relapse, such as mucocutaneous, ocular, osseous, or visceral.

(2) Treatment-resistance, a rare condition manifested by failure of the primary and secondary lesions to respond to adequate mapharsen-bismuth therapy, usually accompanied by the presence of living treponemes in the lesions.

(3) Serologic relapse as evidenced by reversal of a negative STS (serologic test for syphilis) at the conclusion of mapharsen-bismuth therapy to positive during the 6 months post-treatment observation period. Criteria of serologic relapse are discussed in paragraph 7*b*.

(4) Serum-fastness as evidenced by a persistent positive STS at the end of mapharsen-bismuth therapy.

d. Treated primary secondary, and latent syphilis intolerant or sensitive to mapharsen-

bismuth therapy. This group includes individuals who have had a serious reaction to arsenic that contraindicates its further use. Jaundice, exfoliative dermatitis, a blood dyscrasia (thrombocytopenic purpura, agranulocytosis, aplastic anemia) and encephalopathy are examples of such reactions. Patients who manifest persistent intolerance of less serious character, such as severe headaches, nausea, vomiting, and diarrhea, even with reduced doses of mapharsen, may also be included.

3. TECHNIC OF PENICILLIN TREATMENT OF SYPHILIS. *a. Facilities and personnel.* Penicillin therapy requires hospitalization of approximately 10 days, including 7½ days of therapy, and time consumed for pretherapeutic diagnostic procedures and administrative details. It is the responsibility of the medical officer in charge to see that adequate supplies of the drug are on hand before actual treatment of the patient is started.

b. Dosage and technic of administration of penicillin. Uniform dosage and technic will be used in all cases. The total dosage will be 2,400,000 units of penicillin, given in 60 consecutive *intramuscular* injections of 40,000 units (2 cc of penicillin solution) at 3-hour intervals day and night for 7½ days. Any convenient time schedule may be adopted, but in most Army hospitals the most suitable schedule is 0200, 0500, 0800, 1100, 1400, 1700, 2000, and 2300. The solution should be injected intramuscularly into the upper outer quadrant of alternate buttocks. The needle should be 2 inches to 2½ inches in length, preferably 20-gauge, in order to insure intramuscular injection rather than injection into fat. *No additional antisyphilitic therapy is to be given during or after the completion of the course of penicillin except in the case of penicillin treatment failures discussed in paragraphs 7 and 8 below.*

c. Noninterruption of penicillin treatment. Treatment should continue without interruption after its initiation. On the first day of treatment, commonly, and during the course of treatment less frequently, minor reactions may be encountered. None of these is indication for the discontinuance or interruption of therapy. There have been no instances so far in which it has been necessary to discontinue or interrupt the treatment schedule.

4. REACTIONS OBSERVED IN PENICILLIN TREATMENT OF SYPHILIS. *a. Herxheimer reactions.* These occur frequently in cases of primary and secondary syphilis, less commonly in cases of latent syphilis, and rarely in cases that have already received some antisyphilitic therapy. The manifestations may be focal or systemic and are ascribed to the massive destruction of treponemes in the syphilitic lesions and in the blood stream. These reactions may therefore be considered of favorable significance. Both the focal and systemic Herxheimer reactions are encountered on the first day of treatment only. They begin usually some 3 to 6 hours after the first penicillin injection, gradually become worse and reach a peak, after which they slowly and progressively subside, disappearing within an average of 24 hours. No specific therapy is required although such drugs as aspirin and codeine may be given for relief of symptoms. It must be emphasized that these symptoms disappear spontaneously in spite of the continued, regular administration of penicillin, and are not justification for discontinuance of therapy.

(1) The focal Herxheimer reaction consists of an aggravation of the existing syphilitic lesions. There may be increased swelling of the chancre, further enlargement of already enlarged regional lymph nodes accompanied by pain, and exaggeration of the secondary eruption. A pallid, sparse, macular eruption often becomes extremely profuse and vividly red, and may resemble measles or scarlet fever.

(2) The systemic Herxheimer reaction may be manifested by a variety of symptoms, such as headache, malaise, nausea, occasionally vomiting, abdominal cramps, and weakness, but its most characteristic features are chilly sensations and fever. Peak temperatures of 105.4° F. have been recorded, although generally lower grades of fever prevail.

b. Other reactions due to penicillin. Other reactions caused by penicillin have been extremely rare and trivial in the dosages recom-

mended in this bulletin. Most patients will complain of more or less local muscle soreness at the site of the injections, but usually this has not been objectionable. The most common late systemic reactions have been secondary fever occurring toward the end of treatment and terminating immediately on its cessation; urticaria or other minor skin eruptions; generalized pruritus; herpes labialis and progenitalis; and mild gastro-intestinal symptoms such as abdominal cramps, nausea, and occasionally vomiting.

5. POST-TREATMENT OBSERVATION OF PATIENTS TREATED FOR SYPHILIS WITH PENICILLIN. *a. Serologic and clinical follow-up.* All syphilis cases treated with penicillin will have a monthly inspection and quantitative STS for a period of 12 months. In theaters of operation suitable alterations of this plan may be adopted.

(1) *Laboratory technic.* In patients treated for syphilis with penicillin laboratory procedures will be performed in the local Army laboratory wherever possible. In those situations where no Army serologic laboratory is locally available, blood serum and spinal fluid will be shipped to a service command laboratory. The service command laboratory will provide on request special merthiolated tubes for the shipment of specimens of blood serum and spinal fluid.

(2) *Quantitative serologic tests for syphilis.* On each specimen of blood the laboratory should be requested by the medical officer to perform the authorized quantitative STS, described in TM 8-227, and to report the result in units.

b. Spinal fluid. (1) In primary and secondary syphilis the spinal fluid will be examined as soon after the completion of 6 months of observation as feasible. In no case will the syphilis register be closed until this examination has been accomplished.

(2) Spinal fluid tests to be performed. Cell count; Pandy or Nonne-Apelt qualitative tests for protein; quantitative estimation of total protein; complement fixation (Wassermann) test, or, if this is not feasible, a flocculation test; and colloidal gold test. The cell count and Pandy or Nonne-Apelt test should be performed at the local laboratory within 30 minutes after the spinal fluid is withdrawn.

c. Special administrative features of penicillin treatment. (1) Preparation of the Syphilis Register (W. D., A. G. O. Form No. 8-114) (formerly W. D., M. D. Form No. 78). This will be filled in completely in the usual manner and a brief note describing the treatment procedure will be made in the register. A sample note reads as follows:

> Soldier received intensive penicillin therapy from 20 June 1944 to 27 June 1944 consisting of 60 consecutive intramuscular injections of 40,000 units at 3-hour intervals for a total dose of 2,400,000 units. There was a febrile Herxheimer reaction the first day with peak fever of 102.4° F. Lesions were healed when therapy was completed.

Notation will also be made in the register that patient is to be managed in accordance with TB MED 106.

(2) *Preparation of W. D., M. D. Form No. 78a* (Patient's Record of Syphilis Treatment). This will be prepared as a personal record for the soldier. A brief account of the treatment status of the patient will be entered. This can be done simply by repeating the note made in the syphilis register, described in (1) above. An additional statement will be made to the effect that no further treatment is required, except in the event of clinical or serological relapse, but that the patient will have a regular monthly physical examination and blood test. This form can be used as a record of follow-up and a reminder for the soldier by inscribing at each visit the date set for the next examination.

(3) *Closure of the syphilis register.* (*a*) *Primary and secondary syphilis.* The syphilis register will be closed in primary and secondary syphilis and transmitted to The Surgeon General after 12 months of observation in all patients who have become and remained serologically negative; who have had no evidence of clinical relapse; and who have had a negative spinal fluid between the completion of 6 months of observation and the time of closing of the register.

(*b*) *Latent syphilis.* The syphilis register will be closed in latent syphilis and transmitted to The Surgeon General after 12 months of observation if there has been no clinical or sero-

logic relapse even though the serologic tests have remained persistently positive. It is anticipated that serum-fastness will not be uncommon in cases that receive penicillin therapy in the latent stage of syphilis.

6. CLINICAL AND SEROLOGIC POST-TREATMENT COURSE OF FAVORABLY RESPONDING PENICILLIN TREATED SYPHILIS. *a. Primary and secondary syphilis.* (1) *Clinical course.* The rate of healing of primary and secondary syphilitic lesions varies, depending principally upon the type of lesion. Ordinarily, simple nonulcerated chancres of small size, mucous patches, and macular eruptions are healed by the time the treatment course is completed. Large ulcerated chancres, deeply infiltrated papular eruptions, and large condylomata lata may not heal completely for 1 to 3 weeks after treatment is concluded. Presence of such lesions, unless physically incapacitating, or requiring extensive local treatment, will not be cause for prolonged hospitalization.

(2) *Serologic course.* The titre of the STS declines gradually from positive to negative in the post-treatment period, the negative phase being achieved in a variable time. The majority of cases become negative between the second and fourth post-treatment months, although earlier and later reversals occur. In general, the higher the initial titre of the quantitative STS the longer the test will take to become negative, and the lower the initial titre the sooner the test will become negative.

(3) *Critical relapse period.* The critical period for relapse, both clinical and serologic, appears on the basis of present information to lie between the third and sixth post-treatment months, although relapses have occasionally been observed at earlier and later periods.

b. Latent syphilis. (1) *Clinical course.* Since these patients have no visible syphilitic lesions, no observations as to healing can be made.

(2) *Serologic course.* The serologic curve may take the same course as that observed in primary and secondary syphilis. This is especially true of cases of very early latent syphilis, notably those which have only recently passed from the secondary phase into the phase of latency. On the other hand, individuals with older latent syphilis are likely to exhibit serologic refractoriness, the STS showing either no tendency or little tendency to lose strength. This results in the case having to be classified eventually as serum-fast.

7. DEFINITION OF PENICILLIN FAILURE. Care should be exercised in the determination of failure since patients may develop intercurrent skin eruptions of nonsyphilitic character. Intercurrent infections and smallpox vaccination may produce a temporary elevation of the titre of the quantitative STS. All forms of clinical relapse are generally accompanied by serologic relapse, or by persistently high serologic titres. Treatment failures may be divided into nine categories.

a. Mucous and/or cutaneous relapse is manifested by the appearance of syphilitic lesions of the mouth, genitals, and skin, the latter especially in the anogenital region. There may be lesions of both skin and mucous membranes (mucocutaneous relapse), or of either surface alone. Darkfield examinations should be performed to corroborate the diagnosis. If darkfield examination is negative, repeated quantitative STS should be performed which will reveal a progressively rising titre. In doubtful cases, consultation is desirable.

b. Serologic relapse is manifested by a rising titre of the quantitative STS after the test has become negative or has manifested a previously falling trend. When a serologic relapse is suspected, the patient should be thoroughly and frequently examined, since serologic relapse is usually accompanied or shortly followed by mucocutaneous or some other clinical relapse. Since the titre of the quantitative STS may vary from time to time, as a result of laboratory technic, and in different laboratories, it is not sufficient to accept minor fluctuations in the titre as evidence of serologic relapse. Serologic relapse should be diagnosed only when a series of consecutive tests, performed preferably in the same laboratory, shows persistently increasing titres over a period of 3 to 4 weeks. In the event that a titred test is not available, a change from a doubtful or negative reaction to a persistently positive reaction will be accepted as adequate evidence of serologic

relapse. It should be noted that the titre characteristically rises during, and for a brief period after, penicillin therapy. This elevation is temporary and is not to be considered evidence of serologic relapse.

c. Serum-fastness in primary and secondary syphilis is manifested by a failure of the quantitative STS to show a marked decline within an arbitrary period of 6 months after completion of therapy. Minor fluctuations in the titre may be observed, and also a drop to a lower sustained level, but there is no consistent, gradual, and maintained fall to negative. This condition will be uncommon in primary and secondary syphilis, where it will be considered a treatment failure when present 6 months after completion of therapy. *It will not be uncommon in latent syphilis, in which it will not be considered a treatment failure.*

d. Neurologic relapse (neurorecurrence) may occur as acute syphilitic meningitis, with headache, dizzy spells, fever, and rigidity of the neck. In fulminant cases, coma may supervene rather rapidly. Less commonly relapse in the nervous system may appear as an isolated cranial nerve palsy or paralysis of one or more extremities. Diagnosis should be confirmed by spinal fluid examination. In these cases the neurologist should be consulted for diagnostic assistance.

e. Asymptomatic neurosyphilis is manifested only by an abnormal spinal fluid.

f. Ocular relapse may be manifested by iritis, usually unilateral, or optic neuritis, or neuroretinitis, which may be unilateral or bilateral. The latter conditions may be accompanied by headache, and blurring and progressive failure of vision. In these cases the ophthalmologist should be consulted for diagnostic assistance.

g. Osseous relapse is manifested by severe pain, often nocturnal, in the long bones, most often the tibias, or severe headache when cranial bones are affected. Local tenderness over the affected bone is often very acute. Roentgenograms may assist in the diagnosis.

h. An extremely rare case may occur (none so far observed in 3,000 cases) that is treatment-resistant to penicillin, where lesions fail to heal and living treponemes are present after completion of the treatment course.

i. Other forms of visceral relapse such as hepatitis have so far not been observed but should be watched for.

8. MANAGEMENT OF PENICILLIN FAILURES. *a.* Cases of neurologic relapse and asymptomatic neurosyphilis will be managed in accordance with TB MED No. 48, 31 May 1944.

b. All other forms of treatment failure after the 2,400,000-unit course of penicillin will receive a second course of the drug. This will consist of 4,000,000 units of penicillin, given in 80 consecutive intramuscular injections of 50,000 units at 3-hour intervals day and night for 10 days. These patients will be followed during the post-treatment period as described in paragraph 5. Treatment failures after the second course of penicillin will be transferred to one of the general hospitals designated as a neurosyphilis center in section I, War Department Circular No. 347, 1944, for further evaluation and treatment. In theaters of operations, suitable arrangements should be provided for expert consultation in these cases.

9. TREATMENT OF CERTAIN ARMY AIR FORCE PERSONNEL. Personnel of the Army Air Forces required to participate in frequent and regular aerial flights may be treated with penicillin, as provided herein, under conditions prescribed by the Commanding General, Army Air Forces.

[A. G. 300.5 (29 Sep 4).]

BY ORDER OF THE SECRETARY OF WAR:

G. C. MARSHALL,
Chief of Staff.

OFFICIAL:

J. A. ULIO,
Major General,
The Adjutant General.

SYPHILIS

THE ACTION OF PENICILLIN IN LATE SYPHILIS

INCLUDING NEUROSYPHILIS, BENIGN LATE SYPHILIS AND LATE CONGENITAL SYPHILIS: PRELIMINARY REPORT

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BALTIMORE
AND
W. BARRY WOOD JR., M.D.
ST. LOUIS

These cases are drawn from eight clinics at present engaged in a study of the effect of penicillin on late syphilis, under the general auspices of the Committee on Medical Research of the office of Scientific Research and Development. These, with the names of the responsible investigators, are as follows: University of Pennsylvania (John H. Stokes, M.D.), Cornell University (Walsh McDermott, M.D.), Mayo Clinic (Paul A. O'Leary, M.D.), Boston Psychopathic Hospital (Harry P. Solomon, M.D.), University of Michigan (Udo J. Wile, M.D.), Bellevue Hospital (Evan Thomas, M.D.) and Johns Hopkins University (J. E. Moore, M.D.). Associated with each of them are various co-workers and assistants too numerous to mention here, but to whom due credit will subsequently be given.

Penicillin has distinctly beneficial serologic and clinical effects on neurosyphilis, including early and late manifestations, not excepting tabes and paresis, and including asymptomatic neurosyphilis. Its action on gummatous manifestations of skin, mucosae and bones is so striking and complete that it seems unnecessary to collect further cases merely to demonstrate it as such. In ocular syphilis, simple inflammatory processes respond; later and more complicated lesions such as the optic neuritides and interstitial keratitis recover, relapse, present resistance and residues proportional to damage already done. This statement is probably true of visceral syphilis and of special localized processes and eighth nerve involvement.

These categorical statements are based on a material collected from 182 cases, observed for periods ranging from eight to two hundred and fourteen days after the institution of treatment. The preliminary conclusions are sharply limited by qualifications involving not only duration of observation and small numbers in individual breakdown items but by wide variation in time-dosage relationships and little uniformity as to time and type of test and recheck procedure. No precedents existing, each investigator groped his way into his problem. A considerable part of the material collected from nonuniform records was of such short observation and so "mixed" in therapeutic procedure that it furnished little evaluative worth. The distribution by source, duration of observation and diagnosis is given in table 1. Paresis, a crucial tester of therapeutic effect, heads the list (56 cases) and neurosyphilis totals 122 cases. Observation of sixty days or more was maintained in 44 Pennsylvania, 20 Johns Hopkins, 11 Mayo, 1 Bellevue, 5 New York Hospital and 1 Michigan case, a total of 82 cases.

Notwithstanding the limitations described, the material furnished the basis for demonstrating by both symptoms and laboratory tests (quantitative serologic, spinal fluid examination) the incontestable reality of the effect of penicillin treatment in syphilis. It permits an exploratory breakdown into grades of treatment effect as such, in relation to previous standard treatment; by at least two grades of intensity of penicillin treatment—low intensity (type A) 600,000 to 1,200,000 units of the sodium salt at 10,000 to 25,000 units intramuscularly every three to four hours and high intensity (type B) 2,400,000 to 4,000,000 units at 25,000 to 50,000 units intramuscularly every two to four hours. It was not possible from this material to estimate the difference in effect of hourly variations or unit dose variations, or of intravenous or intraspinal medication.

EFFECT OF PENICILLIN ON THE REAGIN TITER OF THE BLOOD

Irrespective of the system used and in all types of late (excluding latent) syphilis, penicillin causes improvement (reduction) of reagin titer in from about 50 to 60 per cent of 96 late cases in which such data were available (table 2). An initial Herxheimer-like rise or "provocative" effect is observable in about 20 per cent of late cases. Within the period of observation 10 per cent of late cases became completely negative.

In 5 cases of seroresistant syphilis, 1 became negative (low titer to start with) and 4 improved. Herxheimer effect occurred in 1.

In 32 cases of general paresis, disregarding treatment system employed, 16 were serologically improved, 2 reduced to negative.

EFFECT OF PENICILLIN ON THE SPINAL FLUID IN NEUROSYPHILIS

This furnishes probably the most graphic demonstration of the effect of penicillin, because of its multiple quantitative approach. Seven grades of change were

The authors are members of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council.
The work described in this paper was done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and several universities.
Read in a panel discussion on "Penicillin in the Treatment of Syphilis" before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

considered: worse, no change and five grades of improvement as follows: grade 1, reduction in cell count or total protein; grade 2, reduction in both cell count and total protein; grade 3, reduction of cell count, total protein and intensity of colloidal test; grade 4, reduction in cells and protein and in intensity of both colloidal and complement fixation tests; grade 5, return to normal.

In grouping improvements, grades 1 and 2 together were rated as slight, grades 3, 4 and 5 together as definite improvement. Improvement as a whole, however, included grades 2, 3, 4 and 5.

TABLE 1.—*Penicillin Investigation: Late and Miscellaneous Syphilis; Distribution of Material by Source, Duration of Observation and Diagnosis*

Diagnosis	Duration of Observation: Immediate: Less Than 20 Days	20-59 Days	60-99 Days	100-139 Days	140-214 Days	Total Cases
Paresis and taboparesis	11	22	15	4	4	56
Tabes, including primary optic atrophy	6	8	5	2	1	22
Meningovascular neurosyphilis	6	3	3	3	1	16
Asymptomatic neurosyphilis	2	13	8	1	4	28
Benign late skin and bone	4	8	3	0	6	21
Interstitial keratitis	0	5	3	3	2	13
Iritis	0	2	1	0	1	4
Miscellaneous	4	6	5	6	1	22
Total						182
Clinic sources						
Bellevue	1	3	1	0	0	5
Boston	8	8	0	0	0	16
Johns Hopkins	9	23	10	2	8	52
Mayo	7	3	6	1	4	21
Michigan	6	2	1	0	0	9
New York Hospital	1	10	5	0	0	16
Pennsylvania	1	18	20	16	8	63
Totals	33	67	43	19	20	182

TABLE 2.—*Blood Serologic Response to Penicillin*

Type of Syphilis	Herxheimer or Provocative Effect	Improved But Not to Negative	Reduced to Negative	Improvement Temporary	No Change
Late (96 cases)	20	33	10	13	25

TABLE 3.—*Cerebrospinal Fluid Changes Following Penicillin in 107 Cases in Which Repeated Spinal Fluid Examinations Were Available at Some Time After Treatment*

Diagnosis	Slight Improvement: Grade 1 Cells or Protein Reduced	Slight Improvement: Grade 2 Cells and Protein Reduced	Definite Improvement: Grade 3 Cells Protein Colloid Reduced	Definite Improvement: Grade 4 Cells Protein Colloid and Wassermann Reduced	Definite Improvement: Grade 5 Return to Normal	No Change	Worse
Paresis and taboparesis (42 cases)	6	19	4	4	0	5	4
Tabes and meningovascular (25 cases)	4	2	4	7	0	5	3
Asymptomatic (40 cases)	7	5	6	9	1	6	6
Total (107 cases)	17	26	14	20	1	16	13

In a total of 107 cases which had had one or more spinal fluid examinations after completion of penicillin therapy, it appears that 78 cases showed some degree of improvement in spinal fluid findings, 43 slight and 35 definite. The commonest change is a reduction in cells and total protein, but grade 4 improvement is remarkably common, including all four items of the fluid examination. This response is, as would be expected, evident in a higher proportion (1/4) in asymptomatic neurosyphilis than in paresis (1/9). Some of the cases rated as "worse" are, we believe, to be regarded as Herxheimer or flare effects and would probably improve on longer observation. It is interesting that 4 asymptomatic cases accompanied by gummatous benign syphilis were among the 6 asymptomatic cases in which the condition became "worse."

In order to carry the specific touch of conviction to the doubter as to the effect of penicillin on the blood and spinal fluid, we reproduce here serial spinal fluid and blood observations of 6 patients, 3 with late con-

TABLE 4.—*Penicillin Treatment Series 1 in Case 3; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid: Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	29	0123	3 plus	4432210000
13	.....	12	0012	2 plus	2211000000
76	2	10	0112	1 plus	3211000000

TABLE 5.—*Penicillin Treatment Series 2 in Case 3; Total Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid: Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
104	16 units	11	0112	20 mg.	2211100000
164	Less than 1	5	0012	20 mg.	2211000000

TABLE 6.—*Penicillin Treatment Series 1 in Case 5; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid: Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	128 units	22	1244	4 plus	1333320000
19	16	8	1244	3 plus	4431100000
55	32	4	0012	Plus-minus	2221000000
86	64	3	0123	20	2221100000
111	64	1	0124	50	2211000000

genital syphilis and 3 with acquired neurosyphilis. It is notable that these effects were secured with low intensity (type A) treatment in all but 1 case.

CASE HISTORIES

CASE 3 (Pennsylvania).—A man aged 38, with acquired syphilis. Primary optic atrophy in tabes, with euphoria, possible taboparesis. Fields (fig. 2) showed sector defect suggesting arachnoiditic or retrobulbar neuritic episode. Original spinal fluid, cells 122, Kolmer Wassermann reaction 4444, Pandy 4 plus, mastic 4442110000, improved to cells 29, Kolmer Wassermann reaction 0123, Pandy 3 plus, mastic 4432210000 by two Swift-Ellis treatments. After the first series of treatments with penicillin (table 4) the patient began to lose ground visually, with slight confusion and increased euphoria. The second series of treatments (table 5) resulted in definite improvement in fields, acuity and mental state.

CASE 5 (Pennsylvania).—A man aged 24 with congenital syphilis with typical stigmas, asymptomatic neurosyphilis, previously treated with forty arsenical and forty bismuth injections, was given the treatment outlined in table 6. He was retreated twenty-eight days later with the results shown in table 7.

CASE 11 (Pennsylvania).—A man aged 18 with congenital syphilis discovered at age 6 and treated with thirty neoarsphenamine injections a year for eleven years showed typical stigmas, neurologic signs, including Argyll Robertson pupils, anisocoria, partial ptosis of the left eyelid, weakness of the left seventh nerve and sluggish reflexes. He was given the treatment outlined in table 8. The ptosis disappeared under penicillin.

CASE 8 (Pennsylvania).—A woman aged 41 with acquired asymptomatic neurosyphilis discovered in blood donation, without symptoms or previous treatment, was given penicillin with the results shown in table 9.

CASE 29 (Pennsylvania).—A woman aged 29 with acquired neurosyphilis experienced sudden diminution of vision, advanced primary optic atrophy. Previous treatment, 1935-1939, consisted of eighteen arsphenamine and thirty-six bismuth injections. Treatment with penicillin (table 10) resulted in no improvement in fields or acuity: right eye 20/400, left eye 20/300.

CASE 50 (Pennsylvania).—A man aged 25 with congenital syphilis, showing typical stigmas and asymptomatic neurosyphilis, had been treated with sixty-two injections of neo-

TABLE 7.—*Penicillin Retreatment Series 2 in Case 5; Total Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
139	64 units	2	0011	40	2211000000
164	64	4	0011	20	1111000000

TABLE 8.—*Penicillin Treatment Series 1 in Case 11; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	32	1244	4 plus	3332210000
13	4	16	0122	1 plus	2111000000
32	4	8	0011	Plus-minus	1111000000
140	Less than 1	1	0000	30 mg.	1110000000

arsphenamine and 102 injections of bismuth. Results of treatment with penicillin are shown in tables 11 and 12.

CASE 64 (Pennsylvania).—A man aged 37 with acquired syphilis, early paresis (?), showed sluggish pupils and lower cord reflexes and loss of memory. Previous treatment consisted of twenty-two mapharsen injections and nineteen bismuth injections.

SYMPTOMATIC RESULTS IN NEUROSYPHILIS

Since there is a well recognized disparity between symptomatic and serologic response in neurosyphilis, and the symptomatic often outweighs the serologic aspect in importance for the patient, symptomatic responses secured by penicillin in neurosyphilis were next examined. Here it is important to give warning of misinterpretations due to Herxheimer and possibly therapeutic paradoxical effects from overintense initial treatment. It is notable that some patients who did badly at the start improved later and that top notch symptomatic gains followed a low intensity system in some cases.

Penicillin also has a favorable effect in general paresis. Three groups were made up from the material (conceding the inadequacy from the psychiatric standpoint due to record deficiencies): simple demented paresis (grades 1, 2 3); deteriorated paresis (grades 1, 2, 3); progressive paresis (galloping and so on) and symptomatic exacerbation suggesting Herxheimer effect. Improvement was graded 25, 50 and 75 and 100 per cent, the last representing practically complete restoration to normality.

Of 56 cases of paresis and taboparesis, 10 presented no adequate classification data. Of the 46 remaining cases 30 were classified as simple demented, of which

TABLE 9.—*Penicillin Treatment Series 1 in Case 8; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	64 units	103	4444	4 plus	2444411000
17	8	29	1244	2 plus	2221100000
46	32	11	0012	1 plus	2211000000
74	32	6	0112	30	1111000000
102	32	6	0112	40	2211000000
129	8	4	0011	30	1111000000
159	32	8	0122	30	2211100000
178	16	6	0012	30	2221100000

TABLE 10.—*Penicillin Treatment Series 1 in Case 29; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	64 units	148	4444	30 mg.	3331100000
9	64	16	1244	30 mg.	2221100000
30	32	15	0012	30 mg.	2221000000
65	64	4	0122	20 mg.	1111000000
119	32	0	0011	20 mg.	1111000000

TABLE 11.—*Penicillin Treatment Series 1 in Case 50; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	96	4444	40 mg.	2455555421
8	Negative	21	4444	20 mg.	4443210000
36	32	12	0124	30 mg.	2221000000

TABLE 12.—*Penicillin Retreatment Series 2 in Case 50; Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
53	Negative	9	0112	30 mg.	2221100000
84	16 units	3	0000	20 mg.	1111000000

TABLE 13.—*Penicillin Treatment Series 1 in Case 64; Total Dose 2,850,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	Less than 1 unit	72	4444	40 mg.	3555521000
22	00	5	0011	20 mg.	1111000000
56	00	5	0012	20 mg.	1111003000

only 6 (20 per cent) failed to improve and 1 grew worse. Thirteen, or nearly half, improved 50 per cent or more, including 8 which improved 75 per cent and 1 restored symptomatically to normal. Ten cases improved only 25 per cent. As might be expected

deteriorated cases (10) made less response, 1 improving 50 per cent, 2 75 per cent and 7 showing no change. The 1 patient with progressive or galloping paresis in Solomon's service died and 1 of Moore's simple demented patients died thirteen weeks after penicillin.

We know of no record of spontaneous remission under the good effects of hospitalization which can

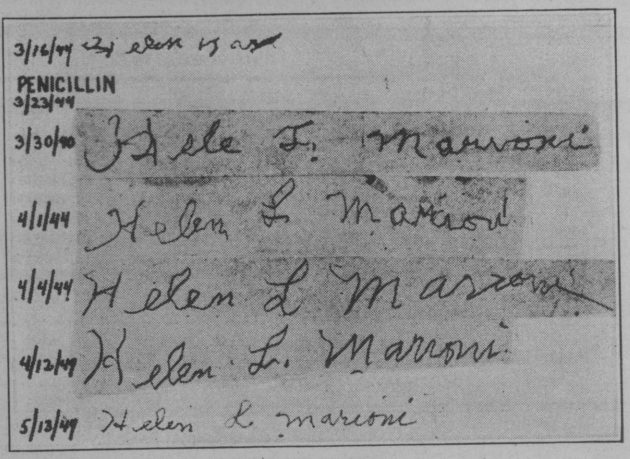

Fig. 1.—Improvement in handwriting of a simple demented paretic patient approximately six weeks after penicillin treatment. The signature before treatment is given above the word "penicillin" (courtesy of George D. Gammon, M.D.).

approach this. The transformations in orientation, speech, handwriting and encephalographic findings will be more fully presented from the University of Pennsylvania material in objective form by George D. Gammon, M.D., in a forthcoming paper. From the collected records, however, two brief summaries are given:

A white woman aged 34 with symptomatic paresis, grade 4 cerebrospinal fluid, could not write or do housework. She had auditory hallucinations, personality changes, disorientation, tremor of the tongue, hands and mouth, and slurred speech. On the second day of penicillin therapy she had a Herxheimer reaction with right-sided convulsions becoming generalized. After twenty-four hours penicillin was reinstituted at half dose to a total of 1,200,000 units without untoward effect. By the sixteenth day the patient was completely oriented, with memory, speech, tremor and electroencephalogram improved. In four months the patient was tremor free, speech and writing were normal (fig. 1), she was well oriented and hallucination free and was satisfactorily performing housework including marketing with points and driving a car. Clinical improvement was not accompanied by improvement in the spinal fluid.

A white man aged 42 with symptomatic paresis developed mispronouncing of words, garbled speech, uncertain gait, tremor of hands and difficulty in writing in August 1943, when a shell exploded near him. Forty-eight arm and hip injections were given. He became boastful, speech rambled and tremors were more pronounced; handwriting was worse and calculation poor. His condition was unimproved during hospitalization after 50,000 Oxford units per dose of penicillin to a total of 4,000,000 units. Clinical improvement occurred three weeks after penicillin with loss of tremors, improved handwriting and speech. He passed an examination as a pipe fitter. Improvement in the cerebrospinal fluid did not accompany clinical improvement. The neurologist considered him mentally improved but not to the original level.

Combining all types of clinically diagnosed paresis and taboparesis, exclusive of 10 patients treated with intraspinal or intravenous penicillin or malaria and thus totaling 46 cases, 15 failed to improve, 12 improved 25 per cent, 6 improved 50 per cent, 10 improved 75 per cent, 1 recovered and 2 died. Of 22 patients with tabes dorsalis, 14 presented data sufficient for interpretation, including 7 with primary optic atrophy and 3 with lightning pains of unusual severity plus 4 taboparetic patients with lightning pains who were grouped together with respect to this symptom. Of the 14 tabetic patients 3 improved to the extent of 50 per cent or more, and 2 of them with lightning pains were relieved completely. Eleven tabetic patients showed no change. Of the patients with primary optic atrophy none were made worse, and 1 whose visual fields are shown (fig. 2) improved slightly but definitely in both fields and visual acuity, with concomitant improvement in the spinal fluid. There is some question as to whether the sector defect in the left field is not a residue of a retrobulbar neuritic process. Of the total of 7 patients with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 was unchanged and 1 became worse.

Of 16 patients with various forms of meningovascular neurosyphilis, 6 presented no data on clinical improvement. Of the remaining 10, clinical improvements of 75 per cent were observed in 2, 50 per cent in 2 and 25 per cent in 2, with 3 showing no change and 1 becoming worse.

It is of course difficult to evaluate symptomatology into which elements of the subjective and the influence of suggestion, rest, practice (as in eye and station and gait tests) enter. The intervention of trifling or routine medication (as in the eye, for example) with improvement found to have begun before penicillin, and hence

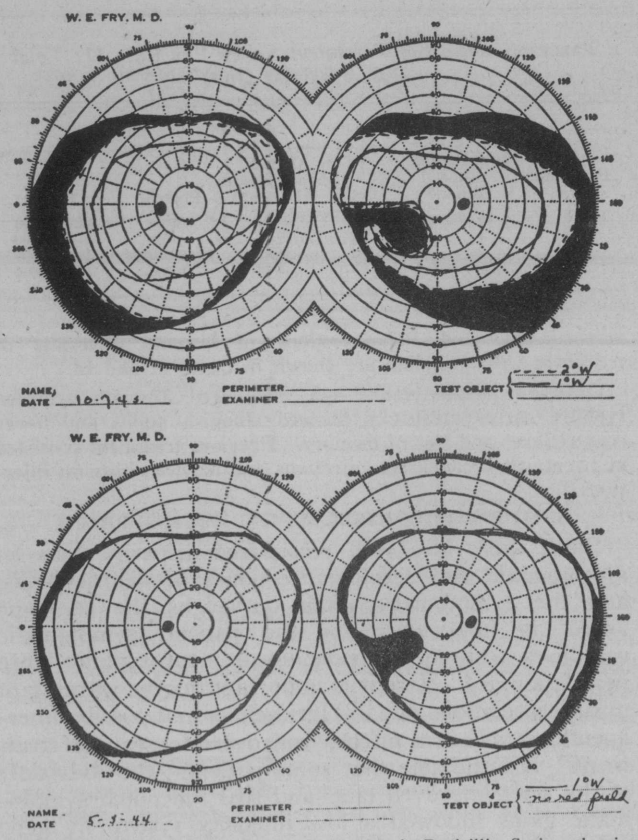

Fig. 2.—Visual fields in case 3, Pennsylvania Penicillin Series, showing improvement with decrease in sector defect.

perhaps merely spontaneous or progressive, must be interpreted by long periods of observation. Symptomatology which is highly complex and of uncertain origin, such as lightning pains, in which the influence of the penicillin on other infective backgrounds may play a part, must be interpreted at this stage with reserve. There seems, however, to be a favorable trend in the

evidence pointing to genuine and indeed rapid good effect on the disease process, supported by such objective detail as handwriting change, encephalograms, disappearance of ptosis and of violent headache associated with meningitis. Coupled with the objective changes in the spinal fluid, such evidence would seem to deserve great weight. It is, however, unreasonable to expect penicillin to restore degenerations and replace neurons.

EFFECT OF TREATMENT SYSTEM

In this material the lack of system in dosage and time intervals reduced the number of cases per recognizable system below statistically usable levels, especially when viewed in relation to duration of observation. Some cases were jumbles of methods and had to be discarded. There were no blood level determinations, and in 3 Mayo Clinic cases spinal fluid penicillin determinations were repeatedly negative. Accordingly, only a study of type A versus type B treatment was attempted, type A representing 1,200,000 units or less, usually at 25,000 units every three to four hours, and type B 2,400,000 units to 4,000,000 units or more at 25,000 to 50,000 every two to four hours. Offhand there was no striking difference recognizable between the effect of shorter time intervals or larger doses except the induction of Herxheimer reactions, which could be avoided by reduction in the dosage of the first twenty-four to forty-eight hours. The analysis of the case material on which treatment information was sufficiently complete for classification, comprising 105 cases, is given in tables 14 and 15.

It must be clearly recognized that such figures as these do not provide for trustworthy therapeutic interpretations. It is particularly in point that the observation periods on the type B (larger dose) treated cases are shorter than those of type A and that a longer observation period may demonstrate a greater efficiency of larger dosage. On the other hand, it is also suggested that in late neurosyphilis good effects may be secured by less than the maximum dosage so far employed. If patients treated with 1,200,000 units in asymptomatic neurosyphilis can achieve almost normal spinal fluids and completely achieve them on retreatment with a similar dosage, a steplike method of successive moderate applications of treatment as distinguished from a single massive session would seem to deserve further study. Pushing the patient over the hump, so to speak, to a partial self cure is a recognized principle in dealing with some aspects of late neurosyphilis.

Serologic response on the blood occurred in 45 per cent of the type A or smaller dose treatment cases, and in 43 per cent of the larger dose or type B cases. Longer observation periods for the type B cases would probably demonstrate a superior effect.

PENICILLIN RESPONSE IN RELATION TO INFLAMMATORY ACTIVITY

Using the cell count and the spinal fluid as a guide and rating 0 to 20 as low, 21 to 60 as medium and 61 and above as high cell counts, an attempt was made to see whether improvement was greater in cases showing a high cell count as an index of definite inflammatory activity in comparison to those showing low cell counts. With cell counts rated as high, improvement occurred in 11 of 31 cases; with those rated as medium, in 13 of 28 cases; in those rated as low, in 7 of 45 cases. It appears that the proportion of improvement is highest in patients with medium and high cell counts in the order named and lowest in patients with low cell counts. If all cell counts above 20 are rated as high, improvement occurs in 24 of 59 cases in the higher cell count brackets (40.6 per cent) and in 7 of 45 in the low cell count bracket (15.5 per cent). Considering the small numbers of cases and the arbitrary division lines, the figures cannot be more than suggestive that, as has been previously indicated, a low cell count has a less favorable prognosis under penicillin treatment than a high cell count.

INFLUENCE OF PREVIOUS (ARSENIC, HEAVY METAL) TREATMENT ON PENICILLIN RESPONSE

An analysis of 100 cases of neurosyphilis with data on this matter yielded the results shown in table 16. The results in this case included grade 1 as well as grades 2, 3, 4 and 5. The type of previous treatment approximated the captions given, the first numeral representing arsenical, the second heavy metal injections.

Almost equally good results in the spinal fluid were achieved by penicillin after no previous treatment and intensive (40-80) routine treatment. There is at least no intimation that previous fever therapy prepared the

TABLE 14.—*Effect on Spinal Fluid of Type A (Small Dose) Versus Type B (Larger Dose) Treatment*

	Grade of Response													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		No Change		Worse	
Type of Neurosyphilis	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Paresis and taboparesis	1	5	2	15	1	2	3	1	0	0	1	3	1	2
Tabes	1	3	0	1	0	1	2	2	0	0	0	5	1	0
Meningovascular	0	2	1	1	1	3	3	0	0	0	0	0	0	1
Asymptomatic	1	6	2	3	1	5	4	5	1	0	3	3	6	0
Grade totals	3	16	5	20	3	11	12	8	1	0	4	11	8*	3
Total type A	36		36		36		36		36		36		36	
Total type B		69		69		69		69		69		69		69

* Four of these patients had benign gummas healing under penicillin at a wholly inadequate dosage for neurosyphilis—less than 600,000 units.
Grade 1 and 2 (slight) improvements occurred in 22 per cent of type A and 52 per cent of type B cases.
Grades 3, 4 and 5 (definite) improvement occurred in 16 of 36 cases (44 per cent) on type A treatment and 19 of 69 cases (27.4 per cent) on type B treatment.
Grades 2, 3, 4 and 5 improvement occurred in 60 per cent of the type A and 56 per cent of the type B cases. The periods of observation, however, were longer in the smaller dose treatment cases—e. g., paresis, over sixty days in type A; less than sixty days in all but 5 in type B cases.

TABLE 15.—*Degree of Cerebrospinal Fluid Improvement*

Type of Treatment	Number of Cases	Slight, Grade 1, 2	Moderate to Definite, Grades 3, 4, 5	No Change or Worse
Type A	36	8 (22.2%)	16 (44.4%)	12 (33.3%)
Type B	68	35 (51.4%)	19 (27.9%)	14 (20.5%)

patients for striking penicillin results. The many qualifications on such an analysis with regard to selection, time of observation and so on must be recalled, but there is at least no strong evidence that in the aggregate previous standard treatment adds anything to the penicillin result.

PENICILLIN IN OTHER ASPECTS OF LATE SYPHILIS

Gummatous lesions of skin and bones (21 cases) respond so invariably and completely, with 13 results rated 100 per cent, 2 at 75 per cent, 4 questionable and only 2 failing of improvement (thirty-six and sixty-eight days), that little further clinical interest attaches to the group beyond speculation as to the part played by penicillin in clearing the secondary, usually hemolytic pyogenic infective invasion as distinguished from the syphilis as such. The control of destructive lesions of the palate and septum seems satisfactory. The failures include one suspected gumma of the orbit, diagnosis not established. The dosage required for symptomatic improvement ranges about 300,000 units, the time for healing from twelve to forty-six days. Carcinoma as a complication or a diagnosis must be watched for even if improvement occurs. Concomitant neurosyphilis was identified in 12 of the 21 cases. Serologic improvement (titer reduction) in the blood occurred in 14 of 21 cases.

TABLE 16.—*Spinal Fluid and Clinical Improvement in Neurosyphilis After Penicillin Treatment in Relation to Previous Treatment*

Type of Previous Treatment	Clinical Improvement Grade 1 and Over Occurred in:	Spinal Fluid Grades 1, 2, 3, 4, 5 Occurred in:
No treatment.....	16 of 32, or 50 per cent	28 of 32, or 87 per cent
Little treatment.....	9 of 23, or 39 per cent	16 of 23, or 69 per cent
20 arsenic, 20 heavy metal.	7 of 16, or 48 per cent	9 of 16, or 56 per cent
40 arsenic, 80 heavy metal.	5 of 16, or 30 per cent	13 of 16, or 81 per cent
Fever therapy.....	1 of 13, or 7 per cent	5 of 13, or 46 per cent

The paradox of gummatous skin and bone lesions healing as the spinal fluid became "worse" (possible Herxheimer effect?) was noted in 3 of 10 cases.

LATE CONGENITAL SYPHILIS

The interest in this group centers on interstitial keratitis. The neurosyphilitic involvements were reviewed with neurosyphilis (see cases 5, 11 and 50). The complexity of interstitial keratitis and the eccentricities of its behavior are apparent under penicillin as under standard treatment. It was difficult to dissuade those in charge of some patients to withhold fever and other treatment if the patient did not immediately and strikingly improve. Patients with pronounced corneal and other ocular damage were included and too much was expected in the way of results. Of 14 cases 6 showed improvement, 3 of grade 4 on a scale of 1, 2, 3, 4, 1 of grade 3 and 2 of grade 2. Six showed no improvement and in 2 the condition was definitely worse. When improvement occurred it was apt to be dramatic. One patient previously given chemotherapy and fever energetically without result was given 1,200,000 units in eight days. He was relieved of photophobia by the third day and returned to work a week after penicillin for the first time in many months. He has remained well, improvement continuing up to the stage of stationary residue. Another improved grade 4 and one hundred and four days after penicillin flared and recovered again without further treatment. A persistently seronegative congenital syphilitic patient with characteristic stigmas made no response and in fact became worse under 1,200,000 units. One of McDermott's patients, a fever failure, received a total of 4,845,000 units in two courses without results. Thomas secured improvement in a case on 4,000,000 units over twenty-five days, 20,000 units every three hours. Moore has excellent serial color photographs of a favorable case. One of his cases likewise improved on 3,970,000 units in twenty-one days, observed for one hundred and fifty-nine days.

OTHER EYE LESIONS

Two cases of optic neuritis on 2,000,000 and 3,000,000 units both showed improvement; O'Leary's case improved 100 per cent on retreatment. Two cases of iritis improved 100 per cent, but 1 relapsed and required an iridectomy for beginning glaucoma, after failing to respond to retreatment.

EIGHTH NERVE DEAFNESS

Eighth nerve deafness, beginning in a woman of 31 with undoubted stigmas of congenital infection, improved somewhat though not definitely on 1,200,000 units. There was a suggestion of Herxheimer-like drop in hearing at the outset followed by improvement, but the interpretations are complex. Two other cases, already far advanced, failed to improve.

MISCELLANEOUS CASES

A scattered group of cases, on which information is incomplete, includes bone-liver combinations, hepatosplenic complexes, seroresistance (Wassermann fastness) already discussed, Charcot hip and gangrenous balanitis in a syphilitic patient. The Charcot hip did not improve, and a suspected Charcot ankle is developing since penicillin. The gangrenous balanitis healed with the loss of less than a third of the corpus spongiosum on 300,000 units at about the rate to be expected of a late syphilid. The patient became seronegative. The livers of 2 patients undoubtedly enlarged (late cases) after treatment and the blood bilirubin increased in 1, then subsided.

REACTIONS TO PENICILLIN

Penicillin is not a reactionless drug. The disposition to pour it about like water in syphilis may lead to serious trouble, especially from therapeutic shock and possibly also from therapeutic paradoxical effects. The former is important under the usual rule that an active syphilitic process in a vital structure may be gravely and even fatally damaged by the impact of a large dose or series of doses at the start of treatment. Most Herxheimer effects, however, seem controllable by reduction in dosage for the first twenty-four to forty-eight hours of an eight day series without loss of ultimate effect. There is some question whether there are not delayed Herxheimer effects such as are suggested by spinal fluid and blood serologic curves and the initially unfavorable but ultimately favorable course of some lesions (eye, nervous system, for example).

Of 182 cases 43 (24 per cent) had reported reactions interpretable as Herxheimer or therapeutic shock effects. Of these 23 were fever, highest 105.5 F. The blood reagin titer increased definitely and then subsided in 7 cases. In 4 Pennsylvania cases symptoms interpreted as Herxheimer effects in the nervous system included transverse myelitic symptoms in 1 case, jacksonian convulsions lasting twelve hours in another, exacerbation of lightning pains, mania and hallucinations.

Other reactions to penicillin included urticaria (2 cases) and 1 each of "allergic reaction," "id" reaction, burning of the skin, profuse sweating and phlebitis (intravenous injection). Two patients had sharp gastrointestinal reactions.

SUMMARY

From a material of 182 cases of late syphilis preponderantly neurosyphilis (122 cases) and including benign gummatous syphilis, ocular and other forms of syphilis and late congenital syphilis, observed from eight to two hundred and fourteen days after the penicillin therapy was begun on a wide range of time-dosage schedules, the following tentative observations are summarized:

1. The lesions of benign gummatous syphilis of skin and bones heal under a dosage of approximately 300,000 units in twelve to forty-six days.

2. Irrespective of the system used, and in all types of syphilis, pencillin causes reduction of syphilitic reagin titer in the blood in from 50 to 60 per cent of late cases. An initial "Herxheimer"-like or provocative rise is observed in about 20 per cent of cases. Only 5 seroresistant cases were treated, 1 made negative, 4 improved.

3. The abnormal spinal fluid in neurosyphilis is improved in 74 per cent to some degree, definitely in 33 per cent. The commonest change is a drop in cell count and total protein (grade 2 improvement on a scale of 5) occurring in 67 per cent of cases. One spinal fluid was rendered normal within the observation period. All four fluid findings improved in 25 per cent of the cases of asymptomatic neurosyphilis, 10 per cent in paresis and taboparesis.

4. Symptoms improved in neurosyphilis as follows: Simple demented paresis: In 30 cases on which data were adequate for classification, 80 per cent improved to some degree; nearly half improved 50 per cent or more, including 8 who improved 75 per cent and 1 restored to normal. Deteriorated paresis: Two of 10 improved 75 per cent, 1 50 per cent, 7 no change. Tabes dorsalis: One fifth of 14 cases improved 50 per cent or more. Of 7 with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 unchanged and 1 worse. Of 7 cases of primary (?) optic atrophy, mostly advanced none were made worse, 1 improved. In meningovascular neurosyphilis 40 per cent improved 50 to 75 per cent.

5. Two attempts at statistical evaluation were made: One, of the influences of smaller dose as contrasted with larger dose treatment and the other, of the response under penicillin of spinal fluids with low as contrasted with relatively high cell counts, because of small numbers of cases and unavoidable disparities in observation period, cannot be accepted as beyond challenge. They suggest respectively that in late syphilis, especially neurosyphilis, smaller doses, if not grossly inadequate, have good effects which may perhaps be improved by repetition, as compared with the effects of initial larger dosage, the effect being due perhaps to stimulation or utilization of the patient's resistance and defensive responses. The figures on response in relation to cell count suggest that moderate and high cell count cases tend to react somewhat better than cases giving low cell counts.

6. Previous treatment for syphilis by older methods in neurosyphilis, including fever therapy, does not appear to prepare patients for superior results with penicillin.

7. In late congenital syphilis, interstitial keratitis presents rather equivocal though at times dramatically favorable results, not as yet interpretable in relation to a time-dosage system. Of 14 cases 6 improved, 3 to 100 per cent, 1 to 75 per cent, 2 to 50 per cent. Two were made definitely worse.

8. Optic neuritis included 2 cases, both improved, the second 100 per cent on retreatment. Two cases of iritis improved 100 per cent at the start, but 1 relapsed and did not respond to retreatment (glaucoma).

9. Two cases of eighth nerve deafness gave equivocal results.

10. Of miscellaneous cases, Charcot joint was unaffected (a new one developing); gangrenous balanitis was cured by low dosage.

11. Therapeutic shock (Herxheimer) effects are undoubted, may be serious in late syphilis and should be guarded against by reduced dosage during the first twenty-four to forty-eight hours. Severe cerebral and cord symptoms may develop in neurosyphilis.

Reactions to penicillin as such are few and not serious, urticaria, itching, allergic skin reactions and a sharp gastrointestinal reaction following the course.

12. It is suggested that, because of the great difficulty in developing uniform records for statistical or punch machine evaluation in late syphilis, further investigation of its behavior under penicillin therapy be committed to individual competent investigators who can apply the principles of uniformity of treatment and record evaluation simultaneously with appropriate individualization of the particular case. The durability of the good effects thus far observed, the possibility of complications from induced allergic response and disturbance of the immunity balance of the individual in latent and late syphilis remain to be explored by larger experience and longer periods of observation.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. MAHONEY, ARNOLD AND STERNER AND MESSRS. HARRIS AND ŒWALLY, OF DRS. MOORE AND MAHONEY, COMMANDER SCHWARTZ, LIEUTENANT COLONEL STERNBERG AND DR. WOOD, AND OF DR. STOKES, LIEUTENANT COLONEL STERNBERG, COMMANDER SCHWARTZ AND DRS. MAHONEY, MOORE AND WOOD

LIEUTENANT COMMANDER E. E. BARKSDALE, MC-V(S), U.S.N.R.: As of June 1, 1944 we have treated 161 cases of syphilis with penicillin. Twenty-nine were seronegative, dark field positive, primary syphilis, clinically cured and are still seronegative to date. Eighty were seropositive, dark field positive primaries. Of this group 2 relapsed within approximately three weeks after treatment was started. The lesions recurred in the same location and again became dark field positive. One of this group healed, becoming seronegative, and then acquired a new infection with a dark field positive chancre in a different location from the previous one. We have treated 31 cases of secondary syphilis. All the cases were treated on a dosage of 1.2 million units intramuscularly, i. e. 20,000 units every three hours for sixty injections. By determining quantitative blood penicillin levels on these patients treated with intramuscular injections every three hours, we found that it was impossible to maintain a constant penicillin level, and indeed for one third of the time there was no penicillin detected in the blood by the test used. This made us think that the continuous intravenous drip method might be the procedure of choice. To date we have treated 11 cases of syphilis by this method, giving a total of 2,080,000 units of penicillin in nine days. With this we were able to maintain a more or less constant blood penicillin level approximately ten times higher than that which could be obtained by the intramuscular route. We have had no

relapses, no central nervous system involvement and no case has retained a positive serologic reaction as yet beyond the fourteenth week. To date we have treated 7 cases of syphilis with the usual routine of fever therapy but substituting for mapharsen 60,000 units of penicillin intravenously each time they were in the fever cabinet. In addition and over the same period of time we gave each patient 20,000 units of penicillin intramuscularly every three hours until a total of 3½ to 4 million units had been given. It is our impression that this method is superior to the one which we had formerly used. I am of the opinion at the present time that penicillin is the best drug we have ever had for the treatment of syphilis. I think that it is possible that the intravenous method of administration may be superior. We have had 1 case of primary syphilis treated intramuscularly with 1.2 million units, which ended fatally ten days after the completion of treatment, of a subdural hemorrhage which was not related to either the syphilis or the treatment. Pathologic examination of body tissues with special stains failed to reveal any spirochetes. At autopsy therefore this 1 case within ten days after treatment gave no pathologic evidence of syphilis.

Captain William Leifer, M. C., A. U. S.: The experience at Fort Bragg now comprises 116 patients treated for syphilis with penicillin. One hundred received 1,200,000 units and 16 received 2,400,000 units in seven and one-half days (technic sixty consecutive intramuscular injections of 20,000 or 40,000 units at three hour intervals). Reactions were infrequent and inconsequential: there were 3 instances of urticaria, 1 of erythema multiforme, 2 of generalized pruritus and 7 of herpes simplex. Focal and systemic Herxheimer reactions appeared on the first day of treatment in 87 per cent of the patients. Only those who received 1,200,000 units and who have been followed at least three months are being reported. Ten patients began treatment in the seronegative primary phase and 12 in the seropositive primary phase. Four have been observed over six months, of whom 3 are seronegative, while the fourth has a doubtful Kahn reaction. All 4 had negative spinal fluids at six months. The remaining 18 patients have been followed from three to six months, and all but 1 are seronegative. Thus, 20 of the 22 cases of primary syphilis have achieved or maintained seronegativity. Twenty-five patients began treatment in the secondary stage of syphilis. Two have exceeded six months of observation; 1 is seronegative and the other has a doubtful Kahn reaction. Both had negative spinal fluids at six months. The remaining 23 patients have been followed between three and six months; of these, 11 are seronegative, 9 still have some degree of positivity of the blood and 3 are definitive failures. Two failures appeared as neurologic relapses (1 with monoplegia, the other with acute syphilitic meningitis) with strongly positive spinal fluid; the spinal fluid had been negative in both of these immediately before administration of penicillin. The third failure was a cutaneous and serologic relapse. Thus, of 25 cases of secondary syphilis 12 are seronegative, 10 are still seropositive and 3 are outright failures. It would seem best to use higher doses than might now appear necessary in the treatment of syphilis. The future may reveal the need not only for an increase dosage but also for prolongation of the treatment period beyond the present seven and one-half days. Thus far the results have been extremely encouraging, but mass treatment of syphilis with penicillin should be delayed until the optimal treatment schedule is determined.

Commander Frank A. Ellis, Corpus Christi, Texas: I should like to give you some of the highlights of the experience with penicillin starting in New Zealand in Wellington and extending up to Corpus Christi. An enlisted man with acute infectious jaundice, after being in the hospital five days, developed an acute gonococcic urethritis. His icterus index was 45, and we gave him penicillin; it cured his gonorrhea, and his icterus index was brought down to 0.5. Penicillin might cure acute jaundice or acute infectious jaundice, as we designate it in the Navy. Our results in probably 450 cases of acute gonococcic urethritis have been 100 per cent effective, with this exception: We had 2 cases in which acute epididymitis developed three days after administration of 100,000 units of penicillin. On those we immediately repeated the therapy and gave them 200,000 units until the smears, urine culture and prostatic cultures were negative. My impression is that it certainly shortens the course of acute epididymitis. Our results have been most disappointing in penicillin therapy for nonspecific urethritis. With syphilis I have had no experience whatever except this, that I want to caution you about intraurethral chancre being masked in acute gonorrhea. If patients are given 100,000 units, the dosage will be inadequate.

Colonel Udo J. Wile, U. S. P. H. S.: It is too much to expect of penicillin at this time more than has been graphically told by the authors. We should accept these facts with the possibility that in time the organisms may elaborate for themselves a certain degree of resistance to penicillin. When we can speak in terms of thousands instead of terms of hundreds, we may have more relapses and more recurrences and possibly more reactions. It is, however, a great relief to those of us who have for years felt that we were using dangerous drugs in the treatment of syphilis to find something at least that departs from heavy metals that gives a high index of therapeutic effectiveness and apparently a low toxicity.

Dr. Joseph E. Moore, Baltimore: I close on the same restrained note of optimism which has been voiced to you here. I don't think that penicillin is ready for mass application. I do feel that our attitude ought to be one of hopefulness, but with complete understanding that we are still in the process of learning how to use the drug. We don't know yet, and it is going to be some time before we are sure.

SYPHILIS

PENICILLIN IN THE PREVENTION AND TREATMENT OF CONGENITAL SYPHILIS

REPORT ON EXPERIENCE WITH THE TREATMENT OF FOURTEEN PREGNANT WOMEN WITH EARLY SYPHILIS AND NINE INFANTS WITH CONGENITAL SYPHILIS

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The treatment of the pregnant syphilitic woman and of the congenitally syphilitic infant with weekly injections of neoarsphenamine or mapharsen supplemented by a bismuth preparation, although eminently satisfactory from the standpoint of both preventive and curative medicine, still has several aspects in which improvement may be expected. These facts have led us to try penicillin in the treatment of these conditions with the hope that it might be possible to eliminate some of the deficiencies in present day therapy.

Included among the factors in the prevention and treatment of congenital syphilis which we would like to see improved by the discovery and application of new drugs and new technics, the following may be mentioned:

1. Arsenotherapy is relatively toxic. Although, generally speaking, arsenicals are well tolerated and safe to use in the average case,[1] reactions do occur which interfere with treatment or at times preclude their use entirely, and death of the expectant mother has been known to result from chemotherapy for syphilis during pregnancy.[2] A safer drug is accordingly a desideratum.

2. Antepartum syphilis treatment, as usually administered, is not curative of the mother's syphilis. For this purpose it must be continued for long periods post partum and, in order to prevent the birth of syphilitic infants, it must usually be repeated in each subsequent pregnancy.[3] It is true that intensive arsenotherapy (five day drip) has been employed successfully for a small number of pregnant women with early syphilis,[4] but this approach to the prevention of congenital syphilis is not generally accepted.[5] It is relatively toxic and must be considered dangerous in routine medical practice and a questionable choice even under ideal circumstances. One of the extremely difficult public health and social problems in this field has been the postpartum observation of the mother for syphilis.[6] A drug which would be curative during the pregnancy of both mother and child is to be wished for.

3. Although several short series of cases appear in the medical literature in which 100 per cent normal infants have resulted from adequate arsenotherapy of the syphilitic pregnant woman,[7] larger series show a definite residuum of syphilitic infants sometimes in spite of ideal therapy.[8] This is usually in the neighborhood of 5 to 8 per cent diseased infants if the treatment has approached accepted adequacy. Particularly difficult cases for intravenous arsenotherapy are those in which treatment is not commenced until the latter months of the pregnancy, particularly if the expectant mother is in the early stages of her disease.[9] Under such circumstances a very high percentage of infants are syphilitic in spite of therapy. This problem is bound to the permeability of the placenta, to the arsenobenzene derivatives and to the effectiveness of the uncertain quantities of the drug which do pass from the mother to the child after the fetus in utero has been infected.[10] In such instances the placental membrane must be traversed by a curative dose of the drug if a normal infant is to be born. An effective spirillicide which will readily traverse the placenta is still to be hoped for.

4. Three principal factors still complicate the treatment of infantile congenital syphilis. They are the extreme caution with which therapy must be inaugurated when the disease is manifest,[3] the prolonged course of treatment essential to cure [11] and again the residue of patients who are not cured by arsenotherapy and bismuth, a proportion which increases rapidly with the age of the infant at the time treatment is begun.

In addition, the treatment of the syphilitic pregnant woman and, more than this, the observation of the treated syphilitic woman who subsequently becomes pregnant are both critical experiments in the testing of the effect of the new drug. Since the fetus is intimately associated with the mother and is almost uniformly infected if the maternal syphilis is active and untreated, these circumstances give the counterpart in the human being of the inoculation test of cure in the rabbit or other experimental animal. In the woman the

From the Institute for Control of Syphilis, University of Pennsylvania. This work was done under a contract between the University of Pennsylvania and the Office of Scientific Research and Development, recommended by the Committee on Medical Research.

In addition to the directing investigators whose names appear as authors, the following contributed directly to the observations in this paper: H. H. Perlman, M.D., chief, Syphilis Clinic, Children's Hospital; Elizabeth Kirk Rose, M.D., representing the pediatric staff, and G. D. Gammon, M.D., representing the neurologic staff of the Hospital of the University of Pennsylvania; Virgene Wammock, M.D., and O. M. Carrozzino, M.D., representing the staff of the Syphilis Clinic, Philadelphia General Hospital. Roentgenographic studies were performed by the Department of Roentgenology and Radium Therapy of the Hospital of the University of Pennsylvania (E. P. Pendegrass, M.D., director). Quantitative titered blood serologic tests for syphilis were carried out by Mrs. Verna Mayer Stein, serologist to the Syphilis Clinic, Hospital of the University of Pennsylvania. Attendance follow-up after termination of penicillin treatment was carried out under the immediate direction of Public Health Nurse Dolores Hill Middleton of the staff of the Institute for the Control of Syphilis, University of Pennsylvania.

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ultimate test of cure of her syphilis will always remain her ability to give birth to normal children in subsequent pregnancies, even though no further antisyphilitic treatment is administered.

MATERIAL

The cases used for this report consist of 12 pregnant women with symptomatic early syphilis and 2 with early latent syphilis and 9 infants with early congenital syphilis. None had received any type of antisyphilitic therapy prior to treatment with sodium penicillin.

The first pregnant woman started treatment on Nov. 19, 1943 and was delivered March 20, 1944. The maximum period of observation, therefore, at the time of writing this paper (June 29, 1944) has been for the mother seven and one-half months and for the newborn infant three months. Seven of the mothers had not delivered at the time this material was analyzed.

The first infant with congenital syphilis commenced his treatment on Feb. 8, 1944, so that in this case the maximum period of observation is about four months. All patients treated have been included in this report in order to evaluate the initial response to therapy and the contraindications to treatment, if any.

The material has been drawn from the clinics and wards of several of the Philadelphia hospitals [12] and observations were made by members of the University of Pennsylvania Penicillin Panel under the chairmanship of John H. Stokes, M.D.

RESULTS

In the Pregnant Syphilitic Woman and Her Child.—The clinical response to treatment and the result of delivery in each of the 7 pregnant women who have reached term is summarized in table 1. This table also shows graphically the serologic response to treatment of both mother and child. In each instance an apparently normal infant has resulted at full term except in case 76, in which the infant was considered to be premature because it weighed only 4 pounds 10½ ounces (2,112 Gm.) at birth, but it appeared otherwise healthy. Dark field examination of the umbilical vein was negative in 5 instances and not performed in 2. Roentgenograms of the long bones during the neonatal period performed in 4 cases at birth and repeated at the age of 6 weeks or later in every instance were all normal. Three of the infants had positive cord and neonatal blood serologic tests in every case with quantitative titers either equal to the mother's or lower. In case 13, the mother's blood serologic test was 4 Kline units at birth and the infant's ½ unit; in case 25 the mother's titer was 32 units at birth and the infant's 16 units; in case 49 the mother's and infant's titers were both 64 units.

In each instance in which the infant's blood serologic test was positive at birth it has fallen sharply postnatally

TABLE 1.—*Summary of Clinical Course of Seven Pregnant Women with Early Syphilis Treated with Penicillin #*

Clinical Data	Days After Penicillin	Mother Serologic Test, Kline Units *	Days After Delivery	Infant Serologic Test, Kline Units *
Case 4. B., 17 years. U. of Pa. H.	0	256		
	10	256		
Secondary syphilis	31	64		
Penicillin started 11/19/43	74	64		
Total dose: 1,200,000 units	95	8		
	105	64		
Delivered 3/20/44	115	8	0	Negative
Infant: weight 6 lbs. 1 oz.	122	32	17	Negative
	139	4	45	Negative
Dark field umbilical vein negative, normal physical examination, roentgenogram of long bones normal	175	32	53	Negative
	207	64	74	Negative
	223	8	101	Negative
Case 13. B., 29 years. P. G. H.				
Secondary syphilis	0	128		
Penicillin started 12/16/43	9	128		
Total dose: 1,200,000 units	26	32		
	68	16		
Delivered 3/29/44	89	2		
	104	4	0	0.5
Infant: weight 6 lbs. 2½ oz.	124	16	20	Negative
	141	Negative	37	Negative
Dark field umbilical vein negative, normal physical examination, roentgenogram of long bones normal	159	Negative	55	Negative
	173	0.5	69	Negative
			83	Negative
Case 15. B., 16 years. Pa. Hosp.	0	128		
	10	64		
Secondary syphilis	25	128		
Penicillin started 12/24/43	39	32		
Total dose: 1,200,000 units	60	32		
	74	16		
Delivered 5/15/44	87	4		
	115	0.5		
Infant: weight 6 lbs. 11 oz.	122	Negative		
	136	Negative		
Dark field umbilical vein negative, normal physical examination	143	Negative	0	Negative
	168	Negative	25	Negative
Case 25. B., 18 years. U. of Pa. H.	0	128		
	16	64		
Secondary syphilis	29	64		
Penicillin started 1/10/44	53	64		
Total dose: 1,200,000 units	63	16		
	79	32		
Delivered 4/13/44	94	32	0	16
	103	32	9	4
Infant: weight 6 lbs. 14¾ oz.	114	Negative	20	Negative
	128	2	34	Negative
Dark field umbilical vein negative, normal physical examination, roentgenogram of long bones normal	148	4	54	Negative
	163	Negative	69	Negative
Case 49. B., 21 years. U. of Pa. H.				
Secondary syphilis	0	64		
Penicillin started 2/15/44	8	64		
Total dose: 2,400,000 units	21	128		
	36	64		
Delivered 4/3/44	48	64	0	64
	49	..	1	16
Infant: weight 6 lbs. 5¾ oz.	77	64	29	Negative
	98	32	50	Negative
Dark field umbilical vein negative, normal physical examination, roentgenogram of long bones normal	112	2	64	Negative
	126	2	78	Negative
Case 71. B., 22 years. U. of Pa. H.				
Early latent syphilis	0	128		
Penicillin started 3/31/44	14	64		
Total dose: 1,200,000 units	33	128		
	46	32		
Delivered 6/14/44	60	32		
	76	64	0	Negative
Infant: weight 5 lbs. ¼ oz.	77	..	1	0.5
Normal physical examination				
Case 76. B., 24 years. P. G. H.				
Secondary syphilis	0	64		
Penicillin started 4/5/44	13	128		
Total dose: 1,200,000 units	27	64		
	41	64		
Delivered 6/17/44	54	32		
	69	64		
Infant: weight 4 lbs. 10½ oz.	73	64	0	Negative
Normal physical examination				

12. The Hospital of the University of Pennsylvania supplied 8 cases for this study, the Philadelphia General Hospital 11 cases, the Children's Hospital 2 cases, the Pennsylvania Hospital and the St. Luke's and Children's Medical Center each 1 case.

FOOTNOTES TO TABLE

Symptomatic clinical response in the mother in each instance was immediate.

* Given in Kline units for sake of uniformity. Tests were checked with quantitative Kolmer Wassermann and Eagle flocculation with comparable results.

The seven mothers, as of Sept. 28, 1944, have been followed a maximum of 280 days post penicillin (average 216 days). All have become seronegative except case 4 and case 49 (each less than 1 unit of reagin) and case 71, which retains 32 units. All are clinically normal. Each of the infants has remained clinically and serologically normal for a maximum period of 163 days post partum (average 124 days). One of the fourteen pregnant women mentioned in the text, who was treated with 1,200,000 units of penicillin, developed infectious relapsing lesions just prior to delivery, 122 days post penicillin. (Kolmer Wassermann.)

and has become normal in less than one month. In the period of observation, none have shown any tendency to revert to positive. The remaining 4 infants were born with negative blood serologic tests for syphilis and have remained seronegative up to the time these data were compiled. In the period of observation, only 3 of the mothers have become seronegative: Patient 15 was found to be seronegative ninety-five days post penicillin and forty-seven days prior to delivery, and patient 39, who has not yet reached term, was found to be seronegative seventy-seven days post penicillin and has remained so for two months. Patient 25 was found to be seronegative sixty-nine days after delivery.

In the 7 cases in which delivery has occurred penicillin treatment was started 142, 121, 103, 93, 76, 73 and 47 days respectively prior to delivery or from the fifth to the eighth lunar months of the pregnancy respectively. In no instance was treatment instituted after the commencement of penicillin treatment. In 2 cases threatened abortion, as evidenced by spotting and by lower abdominal cramps, occurred in 1 instance in eighteen hours and in the second case in forty-eight hours after the start of penicillin therapy. The drug was immediately discontinued but resumed in full dosage in twenty-four hours without a recurrence of symptoms. This the only type of reaction that developed in any of our pregnant patients could perhaps be considered to be a form of therapeutic shock (Herxheimer reaction) occurring in a grossly diseased area and would possibly fall in the category of placental shock, described in the older literature and occasionally seen after arsenotherapy administered without preparatory treatment to pregnant women with active syphilis. It would suggest that, in the present state of our knowledge at least, it might be best to reduce the penicillin dosage by three fourths to one half during the first

TABLE 2.—*Summary of Case Records of Five Infants with Early Congenital Syphilis Treated with Penicillin*

Identifying Data	Initial Clinical Findings	Weight on Admission	Total	Per Pound of Body Weight	Duration of Observation After Penicillin	Result
Case 43. P. G. H. Race—B. Sex—♂ Age—42 days Treatment started 2/8/44	D. F.+; skin lesions, snuffles, enlarged liver; roentgenogram: advanced osteochondritis and periostitis; serologic test positive, 120 units (Kline)	6 lbs. 3 oz.	100,000 units	16,181 units	99 days	Living; normal physical examination, normal roentgenogram of long bones, negative serologic test since 5/18/44
Case 47. U. of Pa. Race—B. Sex—♂ Age—18 days Treatment started 2/11/44	Premature snuffles, enlarged liver; roentgenogram: pronounced osteochrondritis and periostitis; serologic test positive, 128 units (Kline)	4 lbs. 7 oz.	80,000 units	18,899 units	16 days	Died 2/27/44; circulatory collapse; possible congenital heart disease; no autopsy
Case 58. Child. H. Race—B. Sex—♂ Age—4 months Treatment started 2/29/44	Scaling skin lesions most pronounced on palms and soles, snuffles; roentgenogram: periostitis of long bones; serologic test positive, 128 units (Kline)	12 lbs. 11 oz.	236,000 units	18,373 units	79 days	Normal physical examination; roentgenogram: periostitis disappearing; serologic test, 8 units (Kline) 5/17/44 *
Case 63. U. of Pa. H. Race—B. Sex—♂ Age—8 months Treatment started 3/3/44	Malnutrition; dysphagia; serologic test positive, 64 units (Kline); roentgenogram not diagnostic	13 lbs.	242,000 units	18,615 units	97 days	Normal physical examination; blood serologic test, ½ unit (Kline) 6/8/44
Case 112. St. Luke's Race—B. Sex—♀ Age—51 days Treatment started 5/29/44	Roentgenogram: osteochondritis and periostitis; serologic test strongly positive; associated gonococcic vaginitis	10 lbs. 8 oz.	111,625 units	10,631 units	8 days	Died 6/6/44; temperature elevation to 104 F.; severe diarrhea and dehydration with weight loss of 3 lbs.; autopsy: gross and microscopic finding of congenital syphilis only

All of the mothers had seropositive latent syphilis and none were treated prior to birth of the infants given in the table.
* This patient developed dark field positive skin lesions on Aug. 24, 1944. The infant never became seronegative, and blood titer rose to 32 units when relapsing lesions appeared. Mother showed no evidence of open lesions at the time of relapse in the infant and was receiving treatment with phenarsine hydrochloride and bismuth subsalicylate. This was considered to be a penicillin failure and the infant was retreated with penicillin.

prior to the midpoint of the pregnancy or in the month immediately preceding term.

Method of Treating the Syphilitic Pregnant Woman.—Each of the pregnant women who have thus far reached term had received 1,200,000 Oxford units as her total dose of sodium penicillin, with the exception of patient 71, who left the hospital without receiving her last two four hourly injections and patient 49, who received 2,400,000 units. Three additional patients who have as yet not reached term also received 2,400,000 units. The injections were given intramuscularly, each dose in approximately 1 cc. of sterile distilled water every four hours around the clock for a period of approximately eight days. The individual four hourly dosage for 10 cases was 25,000 units and for 4 cases 50,000 units.

The clinical response of infectious surface lesions to treatment of the expectant mother was very rapid. Usually, Treponema pallidum disappeared, as determined by dark field examination, in less than eight hours. In no case did the dark field preparation show Treponema pallidum longer than twenty-four hours thirty-six to forty-eight hours of treatment of the syphilitic pregnant woman. We have followed this suggested procedure of reduced dosage during the first forty-eight hours for the last 10 pregnant women treated and have not had an additional instance of threatened abortion.

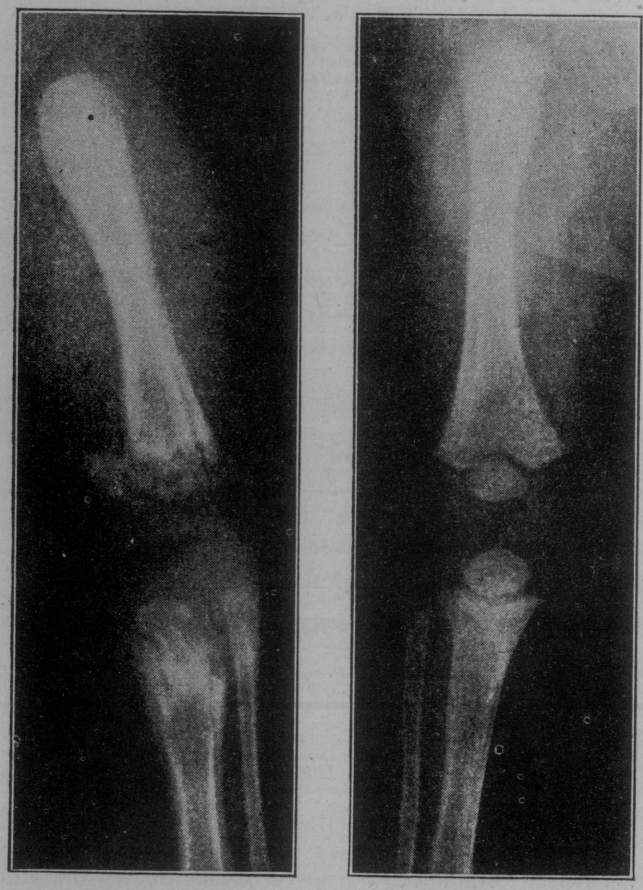
In Infantile Congenital Syphilis.—Nine patients with early congenital syphilis were treated with sodium penicillin. The results in the 3 cases which have been followed long enough to make any report possible are given in table 2. Two deaths possibly not due to penicillin treatment which occurred among 9 cases thus far treated are also included in this table. The 3 living infants followed for 99, 97 and 79 days respectively after administration of sodium penicillin all became clinically normal to physical examination.

All 3 infants had relatively high blood serologic titers initially, but these dropped sharply to normal in 1 instance and to relatively low levels in the other 2 instances (½ unit and 8 units respectively) during the period of observation.

The 2 infants who showed definite roentgenographic changes of syphilitic osteochondritis and periostitis have resumed approximately normal bone development, as shown in the illustration.

Dosage Employed in Infantile Congenital Syphilis.—In 6 of the 9 cases treated, the total dosage of sodium penicillin given every four hours around the clock over approximately an eight day period was between 16,000 and 19,000 units per pound of body weight. This is considerably in excess of the dosage given the majority of the pregnant women, which except in 4 cases was not in excess of 10,000 units per pound of body weight. The remaining 3 infants received respectively 2,935, 10,631 and 11,111 units per pound of body weight.

The only definite treatment reaction noted among the 7 infants who are still living was in the first infant



A. Before penicillin. B. After penicillin.

Improvement in syphilitic osteochondritis from penicillin therapy in case 43, in which treatment was started when the child was forty-one days old. Only the right knee joint is shown, though all the long bones had similar involvement. In *A*, note complete disorganization of distal femoral metaphysis and proximal metaphysis of the tibia. This area is approximately normal in *B*, eighty-three days after commencement of penicillin.

treated (case 43 in table 2). After receiving 19,000 units of sodium penicillin in the first forty-eight hours this patient developed severe dyspnea and cyanosis, necessitating supportive treatment and the administration of oxygen. His condition remained critical during the next eighteen to twenty-four hours, during which period penicillin was withheld. The drug was then resumed in full dosage without recrudescence of symptoms and with apparently a favorable outcome. This is the only infant that thus after a ninety-nine day period has developed a completely negative blood serologic reaction.

COMMENT

Our case material does not permit us to draw sweeping conclusions either as to the management of the syphilitic pregnant woman or with regard to the care of the syphilitic infant. We are of the opinion that the total dosage of penicillin used, the time dose relationship or the duration of treatment employed for our patients is not the ideal. In fact, we are experimenting with other dosage systems. On the other hand, since penicillin is now available for general medical use, it is felt highly desirable to make such factual information as exists available in the medical literature as rapidly as possible.

It is our belief that, as far as it is possible to determine with a limited number of cases, a total dosage of sodium penicillin in the same magnitude (1,200,000 units) as was originally used by Mahoney, Arnold and Harris [13] in the treatment of early acquired syphilis in the adult is safe to use for the pregnant woman, preferably with reduced individual doses for the first thirty-six to forty-eight hours. By safe we mean that it clears the mother of infective surface lesions; with proper time dose relationship it need provoke no after-effects, and it will apparently "protect" a good proportion of the offspring from early or immediate manifestations of congenital syphilis. This is what, plus the danger of other reactions, we had come to expect of the arsenicals. Penicillin may therefore perhaps replace them. In view, however, of the demonstration of an incompletely curative result under 1,200,000 Oxford units in not less than 10 per cent of cases of early syphilis and the trend to higher dosage (2,400,000 Oxford units) on the part of some authorities and competent advisory agencies, we believe that such an advance in the total dose of penicillin is now proper and presumably safe for the pregnant woman in good general condition. By such a total dose, using a therapeutic agent with the reaction-less record of penicillin, we shall, we hope, approach more nearly, if not reach, the cure of the mother with the full protection of the child.

It is not, of course, possible to say whether all the infants in the present series have escaped infection, nor will it be possible so to state short of several years of postnatal observation. It will further not be possible to evaluate the effectiveness of treatment of a syphilitic pregnant woman to prevent congenital syphilis without the analysis of much larger case material observed for a much longer time. It must also be pointed out that the permeability of the placental membrane to penicillin is at present unknown and that cases treated immediately before delivery or prior to the fifth lunar month have not as yet been reported.

There are indications that penicillin given to the mother just prior to delivery (Barksdale) is not recoverable from the umbilical vein at birth. Considering the fact, however, that untreated pregnant women with early syphilis almost uniformly give birth to dead or diseased children, we believe that it is encouraging, to say the least, that among the 14 women treated by us not a single stillbirth or neonatal death has occurred. The 7 infants delivered have, moreover, remained physically normal and seronegative for days of observation numbering 101, 81, 78, 69, 25, 5 and 1 post partum respectively.

We realize that a six months or longer period of active postnatal observation is desirable to rule out the

13. Mahoney, J. R.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**: 355 (Dec.) 1943. Bloomfield, L. A.; Rantz, L. A., and Kirby, W. M. M.: The Clinical Use of Penicillin, J. A. M. A. **124**: 627 (March 4) 1944.

possibility of congenital syphilis. But, if the type of medical follow-up evidence which has been found satisfactory for pregnant women treated with arsenicals is acceptable for those treated with penicillin, then it is distinctly exceptional to encounter congenital syphilis which is not detectable with the use of roentgenographic and blood serologic test procedures by the end of the second month. It seems unlikely, therefore, that the 4 infants who have passed the sixtieth day of postnatal observation will develop signs of congenital syphilis in the future, though we expect to keep them under observation for a matter of years, if possible.

Infantile Congenital Syphilis.—The present state of our knowledge with respect to the ideal treatment of infantile congenital syphilis is much less exact than is our limited knowledge even of the treatment of the syphilitic pregnant woman. Not only are we uncertain that we have developed a proper and effective total dosage or time-dose relationship for the administration of a sodium penicillin to infants with congenital syphilis, but we are in addition not certain that the method of treatment employed by us is entirely safe for the small grossly diseased infant. A word of caution as to the possible dangers of indiscriminate experimentation in this field is therefore given.

It is highly possible that the severe reaction (dyspnea, cyanosis and so on) observed in case 43 would fall into the category of therapeutic shock (Herxheimer reaction). In this instance, in spite of the severity of infection in the infant, little attempt was made to reduce the initial dosage for any considerable time, even though the first three injections (i. e. the first eight hours of treatment) were reduced to one-half the calculated dosage. We are likewise not certain that either of the two observed deaths resulted from the use of sodium penicillin as such. In each instance the death could be accounted for from another cause. In case 47 a possible congenital heart lesion and in case 112 a severe diarrhea with dehydration, uncontrolled by pediatric care, were undoubtedly important contributing factors to the deaths of the infants. In treating congenitally syphilitic infants in the past, however, the reactions caused by injudicious treatment have been considered not infrequently a primary rather than a secondary cause of death.

We believe that it may be significant that each of the infants in whom severe reaction or death occurred was less than 2 months of age. All of the other infants treated were older than 2 months at the time treatment was started. They therefore had had their infections longer, were more fully adjusted to extrauterine existence, had presumably built up some individual resistance and were better able to combat any toxemia which might develop from the too rapid treatment of overwhelming infected body tissue. We are reminded forcefully that the real danger of too energetic arsenotherapy of congenital syphilis lies in these first few weeks of life when the infection is overwhelming, the nutritional state of the infant poor and its resistance to disease undeveloped. We cannot fail to remember also that for complete safety it has been shown that it is necessary to maintain reduced dosage in these cases not for a matter of a few days but often for three or four weeks. Here, then, may be a situation in which too rapid treatment with large dosage of penicillin may be injurious to the infant even though beneficial for the disease itself.

Since the cases described were treated we have observed another infant 2 months old at the inception of penicillin therapy but not reported in detail, since treatment was completed only on June 5, 1944. This infant, which weighed 9 pounds (4.1 Kg.), was given a total dosage of 100,000 units of sodium penicillin in eight days (approximately 11,000 per pound of body weight), but the dosage was kept much reduced from the first to the third day. Five per cent of the total dosage was given in the first twenty-four hours, 10 per cent on the second and third day each and 15 per cent on each day thereafter with no untoward reaction.

In some of the older and heavier infants we have also recently given greatly reduced doses for the first two or three days of treatment without reaction. In spite of this, however, we are not certain that reduced dosage carried out for so short a period will be effective in preventing reaction in every instance if we are here dealing with the type of therapeutic paradox in the small severely infected infant which has accompanied other types of rapidly effective chemotherapy. One necessity for safety certainly stands out with increased emphasis. This is the insistence on painstaking and experienced general pediatric care as an accompaniment to penicillin therapy.

It is too soon to discuss the proof of "cure" of syphilis in women by their ability to bear normal children in subsequent pregnancies, since this is a question which can be studied only over a period of years. If the apparently normal infants born of the women with early syphilis in this study prove on subsequent observation to be nonsyphilitic, then it is a probable but not yet an established fact that these women have been cured of their disease. The most obvious conceivable exception to this supposition would be that the infection was suppressed in the mother as a result of treatment for the several months of her pregnancy in which she was carrying the child to the point where the disease was not transmitted, only to have a recrudescence subsequent to delivery.

It should also be noted that the present report deals with early syphilis complicating pregnancy. It is not certain that these observations are necessarily applicable to the greatest problem confronting the medical profession in this field, namely latent syphilis of unknown duration complicated by pregnancy. It is highly desirable, therefore, that the question of penicillin treatment of latent syphilis complicated by pregnancy be studied as soon as possible.

CONCLUSIONS

1. There are several factors in the medical treatment of the syphilitic pregnant woman and the infant with congenital syphilis which are in need of further study and improvement.

2. It was with the thought that some solution to these problems might be found through the use of penicillin that the present study was undertaken. Sodium penicillin exclusively was employed. Experience with the treatment of 14 pregnant women with early syphilis and 9 infants with congenital syphilis formed the basis for this analysis.

3. The material is reported at this time, even though incomplete, since preliminary observations indicate that sodium penicillin has a definitely good effect both on the mother and on the child in syphilis in pregnancy and on infantile congenital syphilis. Because the drug has been released for general distribution, dissemination of even our present limited knowledge seems desirable.

4. The proper total dosage and the time-dose relationship has not been worked out to complete satisfaction either for syphilis and pregnancy or for infantile congenital syphilis.

5. The limited existing data would seem to indicate, however, that total doses of the magnitude of 1,200,000 Oxford units and 2,400,000 Oxford units given intramuscularly round the clock in approximately eight days, as used in the treatment of early syphilis, are well tolerated by the pregnant woman, with the possible exception that therapeutic or placental shock may occur, to be avoided by considerably reducing the dose for the first thirty-six to forty-eight hours of therapy. The course of expert experience with penicillin in syphilis in general suggests the desirability of the higher dosage (2,400,000 Oxford units).

6. Preliminary results indicate that "cure" or suppression of the infection takes place in a number of the mothers and that miscarriage, stillbirth and neonatal death are averted and the infants are born apparently healthy. It must be reiterated, however, that the period of observation for either mother or child has not been long enough to be certain that they have been cured by the dosages employed. The course of the disease has nonetheless been profoundly and favorably affected.

7. Infants with congenital syphilis make a good response to dosage of approximately 18,000 units per pound of body weight. Grossly infected syphilitic infants, however, may be injured by the injudicious use of penicillin. In the present state of our knowledge their treatment should be approached with extreme caution, with reduced dosage and with great emphasis on proper general pediatric care.

SYPHILIS