# THE TREATMENT OF LATE SYPHILIS, AND OF SYPHILIS IN MOTHER AND CHILD

## A RÉSUMÉ OF PRINCIPLES *

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The problem of the treatment of late syphilis differs in essential particulars from that of early or of true asymptomatic (latent) syphilis. In early syphilis we are still, in spite of the disturbing revelations of Warthin,[1] of Brown and Pearce,[2] and of Eberson,[3] striving for radical cure of the infection. In the late stages of the disease, the problem becomes one of symptomatic improvement and arrest. The early infection usually involves the unimpaired human body. In the late years of the infection the physiologic changes of advancing years are added to the disabilities produced by the action of the disease on vital structures. The characteristic reaction of the body to the syphilitic infection opposes another obstacle to treatment. The slowly progressive fibrosis walls off the organism from the carriers of remedial agents, the blood and lymph. By the induced obliterative endarteritis, the accessibility of foci to spirocheticides injected into the blood or distributed by it is probably materially reduced. In the slowly progressing or latent infection there must also exist a balance between the offensive powers of the organism and the defensive powers of the host. If the organism could be confined within the infected individual and this balance be perfectly maintained, the commensalism would serve all the purposes of the radical treatment methods of the "extirpators." The large majority of late syphilitics have probably effected some measure of compromise with the spirochetal invader, and judgment must be exercised in the disturbance of this relation.

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* Read at the Forty-Fourth Annual Session of the American Dermatological Association, Swampscott, Mass., June 2-4, 1921.

1. Warthin, A. S.: The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or "Cured" Syphilis, Am. J. M. Sc. **152**:508 (Oct.) 1918; New Pathology of Syphilis, Am. J. Syphilis **2**:425 (July) 1918.

2. Brown, W. H., and Pearce, Louise: A Note on the Dissemination of Spirochaeta Pallida from the Primary Focus of Infection, Arch. Dermat. & Syph. **2**:470 (Oct.) 1920; Syphilitic Infection of the Central Nervous System of the Rabbit, Ibid. **2**:635 (Nov.) 1920.

3. Eberson, F.: Dissemination of Spirochaeta Pallida in Experimental Syphilis, Arch. Dermat. and Syph. **3**:111 (Feb.) 1921; Eberson, F., and Engman, M. F.: An Experimental Study of the Latent Syphilitic as a Carrier, J. A. M. A. **76**:160 (Jan. 15) 1921.

APPRAISAL OF POSSIBILITIES AND THERAPEUTIC DECISIONS

The aim of treatment in late syphilis is to carry the infected individual through the fullness of his years, with maximum attainable efficiency and minimum danger to his contacts and to the social order. The first step in the treatment of late syphilis is an appraisal of possibilities, including:

1. An estimate of life expectancy based on age, on damage already done, on the supposed activity and rate of progress of the process, and on its probable refractoriness to treatment.

2. An estimate of the handicaps imposed by complications not directly due to syphilis, such as tuberculosis, nonsyphilitic mental disease, hypertension, chronic interstitial nephritis, diabetes, and so forth.

3. An estimate of the tolerance of the patient for the various methods of treatment available.

4. An estimate of the probable response to treatment of the most vital structures involved.

Treat late syphilis by the indications in vital structures and not in structures nonessential to life. Only a searching examination of the entire body can provide the information for such an appraisal. While the milder forms of treatment may be begun, arsphenamin should seldom be administered until this appraisal is reasonably complete. The inherent crudity of our methods of estimating the condition of many important structures must be remembered and allowed for in making the estimates mentioned. Particularly in involvements of the vascular system is this caution important.

The Herxheimer reaction is as much a feature of late syphilis as of the acute infection. It must never be lost sight of, and the possibility that it will have serious effects, either from the location of the involved structure, as in the case of the larynx or a cerebral vessel, or from its functional importance, as in the case of the myocardium, must be carefully weighed. In general, it is conservative to give all individuals affected with late syphilis mercurial preparation.

The control of infectiousness in late syphilis, while traditionally of little import, deserves more consideration, in the light of recent work on carriers,[4] especially in the woman who is pregnant or may become pregnant, or in the potential father of children. It is, I believe, a good rule that late cases deserve nearly as much arsphenamin as early cases, for the control of this aspect under the limitations imposed by the preliminary survey and the progress of the case.

Adjustments required by the process of healing are factors in therapeutic decisions in late syphilis. When healing begins under treat-

4. Footnote 3, second reference.

ment, the attempt made by the body to compensate for a pathologic change is disturbed, made to take another direction. An adjustment to the effects of cicatricial contracture as well as to the Herxheimer reaction must be made, at times with a paradoxical increase in symptoms, as pointed out by Wile,[5] for syphilitic hepatic cirrhosis. Cicatricial stenosis of the esophagus and rectum, even of the hour-glass stomach, occurs. I am inclined to believe that, so far as the heart is concerned, acute myocardial ischemia, anginal attacks of increased severity, even the development of certain physical signs of aortitis and aneurysm, may be the results of too energetic treatment and too rapid healing.[6]

In the complete appraisal of a case, consideration should be given to the vasculotoxicity of arsphenamin,[7] its hepatotoxicity,[8] and the seriousness of cutaneous exfoliative accidents. At first a theoretic consideration, these items have acquired a very real meaning in my experience with late syphilis. The relatively low toxicity of arsphenamin for the kidney makes it a serviceable drug in nephritis, but there is a notable exception. In low renal function from back pressure, and in pyelonephritis, often a complication of neurosyphilis, it must be used with caution. The history of previous dermatitis as a relative contraindication to arsphenamin does not receive the attention it deserves.

The renotropism of mercury, its ability, by certain modes of administration, to increase the cutaneous reactivity to arsphenamin, its depressant action when overdone and the unfavorable effect on severe

5. Wile, U. J.: Syphilis of the Liver, Arch. Dermat. & Syph. **1**:139 (Feb.) 1920.

6. I was interested to find Hubert (Zur Klinik und Behandlung der Aortensyphilis, Deutsch. Arch. f. klin. Med. **128**:317, 1919) in accord with me on this point.

7. An interesting suggestion that cardiac dilatation after arsphenamin is due to increased pulmonary pressure produced by the obstruction of the circulation or vasoconstriction, and is dependent on the alkalinity of the preparation is made by Smith (Further Pharmacologic Studies on Arsphenamine, J. Pharmacol. & Exper. Therap. **15**:279 [June] 1920). This combined with the observation that neo-arsphenamin is not precipitated in the blood (Schamberg, Kolmer, Raiziss and Weiss: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **1**:235 [March] 1920) would seem to suggest the desirability of neo-arsphenamin in cardiac syphilis.

8. The numerous recent articles on jaundice as a complication due to the toxic action of arsphenamin are reviewed from the standpoint of a possible infectious factor in Stokes, Ruedemann and Lemon's paper (Epidemic Infectious Jaundice and its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:52 [Nov.] 1920. Milian continues his vigorous defense of treatment (Jaundice and Arsphenamin, Médicine, Paris, **2**:113, 1920; abstr., J. A. M. A. **76**:143 [Jan. 8] 1921). Compare also Hallam (Post-Salvarsan Jaundice, Lancet **1**:1356 [June 26] 1920).

anemias, described by Foucar and myself,[9] are among the principal points to be considered. The old-time bugbears of stomatitis, salivation, and gastro-intestinal disturbance have been reduced to relative insignificance by dental prophylaxis, diet, and intelligence in dosage.

As in its resistance to the disease itself the body shows a generous margin of safety, notwithstanding the effect of prolonged or massive treatment, so no symptoms or good recoveries may result from the most flagrant abuse of both arsenic and mercury. But I have always felt that the avoidance rather than the correction of toxic or debilitating effects is the ideal, and to that end have insisted on a number of precautions against complications, which in the end, I believe, protect patients from the small but cumulative insults which too often keep them in a substandard condition under intensive treatment, even though the individual by-effect may not become conspicuous in itself. In late syphilis, in which the margin between treatment requirements and treatment tolerance is often very small, such protective measures may make all the difference between success and failure. In the nine cardinal rules for the management of the excretory mechanism which I shall quote here from my discussion of this point before the Institute for Venereal Disease Control, I should mention that the emphasis on microscopic blood as an evidence of renal damage is drawn from an unpublished study, by Wilder and myself, of the effect of prolonged intensive treatment for syphilis on the kidney. I want also to direct attention to the influence of the atonic bladder with retention symptoms in retarding the progress of patients who would otherwise do well. I am satisfied that the terminal picture in more than one practically arrested but none the less fatal case of neurosyphilis is a composite of depressed renal function and ascending infection of the urinary tract.

### MANAGEMENT OF THE EXCRETORY MECHANISM

1. A cathartic should be given after each arsphenamin injection, and a mild laxative during the course.

2. A weekly urine examination should be the rule.

3. Special attention should be paid to (*a*) casts, (*b*) red blood cells, and (*c*) pus in the urine (catheterized in women).

4. Many or persistent casts mean renal irritation. Occasional showers are not significant.

5. Red blood cells of renal origin mean renal injury.

6. Pus or blood of vesical origin may be an index of cystitis due to urinary retention. In neurosyphilitics with pyuria search should be

9. Foucar, H. O., and Stokes, J. H.: The Effect of Treatment for Syphilis on Severe Anemias, Am. J. M. Sc. to be published.

made for atonic or "cord" bladder with residual urine, secondary cystitis and pyelonephritis, rising blood urea, and falling phenolsulphonephthalein excretion.

7. The excretory mechanism should be protected by (*a*) extirpation of focal infections, (*b*) administration of fluids and alkaline diuretics (*potus imperialis*), (*c*) catheterization and irrigation of neurogenous bladders, (*d*) diet regulation (low proteins), and (*e*) suspension or moderation of treatment if other measures fail.

8. The physician should not discharge a neurosyphilitic patient without being satisfied with regard to his renal function, his blood urea content, and the integrity of his bladder mechanism.

9. Every tabetic patient should be regarded as potentially uremic.

### FACTORS IN A SUCCESSFUL THERAPY

Schamberg, in a personal communication, has suggested that the simultaneous administration of arsphenamin and mercury results in the retention of the arsenic with increased risk of exfoliative accidents.[10] That this retention is so serious as to justify abandoning the simultaneous use of the two drugs I have not as yet been able to convince myself from clinical evidence. Exfoliative accidents in my service come in waves, and have had what seemed to be more than a casual relation to intercurrent and focal infection.

The "broken immunity" of arsphenamin-treated early syphilis, long familiar in clinical experience and now experimentally verified by Brown and Pearce,[11] has, I believe, occasional homologs in late syphilis.[12] All of you have no doubt seen the marked acceleration of the unfavorable progress of some cases of neurosyphilis following arsphenamin, scarcely explainable as mere arsenic fastness. I believe it is a conservative practice never to terminate a period of treatment with arsphenamin, but to finish with mercury, if it be only by mouth.

In early syphilis, symptoms have little meaning as therapeutic guides; in late syphilis they may be supremely important; in fact, their disappearance may be the sole criterion of successful therapy. Eighty-five

10. Klauder, J. V., and Kolmer, J. A.: The Urine in Syphilis. Report of Laboratory Studies, Including the Wassermann Reaction, in Sixty Cases, J. A. M. A. **76**:102 (Jan. 8) 1921.

11. Brown, W. H., and Pearce, Louise: The Resistance (or Immunity) Developed by the Reaction to Syphilitic Infection and Some of the Effects of the Suppression of this Reaction, Arch. Dermat. & Syph. **2**:675 (Dec.) 1920.

12. The unfavorable effect of minute dosage is discussed by Bronfenbrenner, J., and Schlesinger, M. J.: Generalized Infection in Syphilitic Rabbits Resulting from the Inadequate Salvarsan Therapy, Proc. Soc. Exper. Biol. & Med. **18**:94, 1920.

per cent. of late syphilitics, in our experience, selected with only a reasonable degree of discrimination as to therapeutic outlook, should undergo symptomatic arrest and be ultimately placeable on observation.[13] One is occasionally disconcerted by the symptomatic Herxheimer flare-up which dominates the picture during the first three or four weeks of a moderately intensive course. The changes in the Wassermann reaction, while of interest, are not the sole evidence of the efficacy of a method of treatment, and are in fact at times not even an important consideration. In general, a persistent positive reaction is a signal for a rechecking of the fundamental examination and appraisal of the case, and a Wassermann relapse calls for more treatment in the absence of contraindications.

A legitimate distinction should be drawn, in estimating the progress of late syphilis under treatment, between scars and evidences of activity. It is a matter of little moment that a tabetic patient does not recover his knee jerks or a patient with cardiac disease get rid of his aortic murmur. On the other hand, it is decidedly in point if anginal attacks increase in frequency in coronary sclerosis, or if a patient with diffuse hepatitis has a recurrence of jaundice, or the liver fails to decrease in size. Paradoxical pictures at times occur, in which the signs representing scars become more conspicuous as the symptoms representing functional impairment disappear. Ascites developing in hepatic cirrhosis under treatment,[5] bone sequestrums discharged through a sinus, atrophy of the optic nerve as a marked neuroretinitis involutes, pulsation in an aneurysm as the periaortitis subsides, are examples in point. Failure of structural improvement to occur even with marked symptomatic improvement is familiar enough in aneurysm and gastric syphilis. Functional improvement may also outstrip all expectations based on the recognized structural change, particularly in inflammatory processes. In the eye and ear, gains in sight and hearing sometimes have a qualitative rather than quantitative character and may again exceed all expectations.

How far shall treatment be carried after the disappearance of symptoms when the signs are not such as to furnish a guide to the progress of the case? In general, I should say to the point of giving as much treatment as in an early case, provided tolerance permits. This is a vital proviso. The abuse of a patient's tolerance of treatment in late syphilis even more than in early syphilis is, I believe, a serious error, since it is impossible to predict that the course of his infection may not be such that he will be under treatment at intervals all his life. On the

13. Stokes, J. H., and Busman, G. J.: A Clinical study of Wassermann-Fast Syphilis, with Special Reference to Prognosis and Treatment, Am. J. M. Sc. **160**:658 (Nov.) 1920.

other hand, timidity in using effective measures may be precisely the thing which projects the patient onto the other horn of the dilemma. It is for these reasons that I lay much stress on the use of every available means in late syphilis to improve the general status of the patient and to protect him specifically from therapeutic by-effects. When objective guides to the effect of treatment exist, I have found it well to persist beyond the first negative finding, so as to prevent relapse. The question as to whether relapse can be indefinitely postponed by this means remains as yet unsettled. In general, I prefer mercury for the supporter of the resistance that prevents relapse, but I have seldom felt it necessary to urge the life-long "forty rubs a year" if the patient would consent to periodic complete examination. Dismissal of the patient with any such blanket directions seems to me to lay him open to all the uncertainties of an infection kept below the threshold of his own observation by self-medication.

The therapist, in late syphilis, must modify a symptomatic outlook with a preventive trend of mind. This will stimulate him to more complete examination, with a view to finding all the types of involvement in a given case.[14] It will lead him to regulate the life of his patient so as to put the least possible strain on his weakest points, and to conduct his treatment so that an involvement just in its beginnings may not come to the front later as some more conspicuous symptom subsides.

The therapeutic test is so much more important in late syphilis than in early infections that attention should be called to some of its pitfalls. Therapeutic tests in general have meaning only when the patient presents a definite, and, as far as possible, a visible pathologic lesion, on which quantitative estimates of improvement can be made. Mere gain in weight, disappearance of indefinite pains, malaise or nondescript subjective symptoms are usually meaningless. Iodid therapeutic tests, popular with the departing generation, are untrustworthy. So are arsphenamin therapeutic tests. I have made, and seen made, erroneous diagnoses of gumma of the lymph nodes with partial positive Wassermann tests. I have seen tuberculous keratitis confused with syphilitic keratitis, lupus vulgaris, erythematous lupus, sarcoids, and tuberculids make striking improvement under arsphenamin. Mercury is probably more nearly immune from such nonspecific effects than either iodids or arsphenamin, although it is well to recall its action in lichen planus, and in occasional cases of sporotrichosis. Carcinoma of the stomach makes false responses to arsphenamin alone and sometimes in combination with mercury. One of the reasons a noted neurologist gave for object-

14. Studies of the multiform types of involvement often presented by patients with late syphilis seem to have been made largely by internists concerned with cardiovascular conditions. Compare also Footnote 13.

ing to the dermatologist as a syphilographer was his ignorance of the false positive therapeutic test for syphilis in multiple sclerosis. Pseudo-Herxheimer reactions in tuberculous processes occasionally create a deceptive effect.[15]

### STANDARDIZATION OF TREATMENT

Standardization and routinization of the treatment of syphilis is much easier in the early months or years of the disease than in the late. Yet I would not for a moment substitute unlimited individualization for the good effects of system and regularity in the majority of cases. But back of any systematizing of treatment must lie a willingness to think of the disease as a whole, and of the patient as a human being. I have already sufficiently emphasized, in referring to the complete examination, the need of identifying every type of involvement in a given case. The same emphasis can be transferred to therapeutic management. In explaining to patients why I wish their eyes, teeth, tonsils, stomachs, bladders, and appendixes to have attention when their trouble is syphilis of the heart or of the liver, I often use the maxim of the service chief of the best automobile repair plant I know: "Don't listen to the owner's story about this creak and that rattle, and go by that. Go through the car and put her back as nearly as possible into the shape she was in when she left the factory." Do that with late syphilis and it will not need the experimental studies of a Brown or a Pearce to teach you that the course of syphilis is often as much modified by the things we leave undone as by the things we do. Bring the patient, in the course of your management of his case, as nearly up to the standard of normality for his age and sex as possible. Do, so far as possible, an overhauling and not a patching job.

In my few words concerning organized treatment I shall not even attempt an account of the endless variations proposed by different therapists. I do want to suggest, however, that we bear in mind a few principles. First, a heavy responsibility rests on the proposers of systems. Nothing is more eagerly sought after nor more frankly abused by the tyro, and even by the expert, than the rule of thumb. Yet, on the other hand, if there is any one factor which in my experience prevents the arrest or cure of syphilis, it is desultory and unsystematic management. In late syphilis, I believe, roughly speaking, in trying for radical results by combined spirillicidal and resistance-building methods,

15. The original observations on this point have been confirmed by my experience, Herxheimer, K., and Altmann, K.: Weitere Mitteilungen zur Reaktion des Lupus vulgaris nebst Beiträgen zur Therapie desselben durch Salvarsan, Arch. f. Dermat. u. Syph. **110**:249, 1911; Ueber eine Reaktion tuberküloser Prozesse nach Salvarsaninjektion, Deutsch. med. Wchnschr. **1**:441, 1911.

rather than by the one or the other exclusively. Whether we obtain radical results or not, only time can decide. Life-long arrest means almost as much to the patient as extirpation. A frankly spirillicidal technic such as that of Pollitzer [16] seems to me inapplicable to most of the cases which I am considering. I do not feel that its ability to reverse the Wassermann test, so frequently mentioned, is full and sufficient evidence of its effectiveness. It is too difficult to judge the extent and the type of involvement of important structures, even with the most careful preliminary examination, to justify a system of unqualified therapeutic bludgeoning. Recent continental opinion seems to be increasingly tending toward moderation, especially in the early months of the treatment of late syphilis.[17] For the occasional patient with a high resistance to treatment and a threatening, though not as yet actually grave lesion, shortening of the intervals between arsphenamin injections, with large doses, is justifiable in endeavoring to reach an otherwise inaccessible focus. The favorable reports of users of such methods as Sicard's,[18] with its enormous total and minute individual dosage, and the enthusiasm of the "Pollitzerizers," with their enormous individual and relatively small total dosages, are really tributes, not to any individual system, but to the wonderful variability of the disease and to that wide margin of safety for most patients, which enables almost any system that does not grossly violate the few outstanding rules of the game, to tip the delicate balance between progress and arrest, in the favorable direction. To my mind the essence of the modern treatment of syphilis is system and observation, and in the end those of the modern treatment technics which best perfect the *observational* aspect, will show the lowest ultimate mortality.

### TREATMENT OF SPECIAL TYPES

May I, in a series of idiographic sentences, lay before you some of the high points of my observations on the treatment of special types of late syphilis?

16. Pollitzer, S.: The Principles of the Treatment of Syphilis, J. Cutan. Dis. **34**:633 (Sept.) 1916; Ormsby, O. S.: A Valuable Method of Employing Arsphenamin in Syphilis, J. A. M. A. **75**:1 (July 3) 1920.

17. This is especially true, of course, of vascular complications. Compare Kothny and Müller-Deham (Zur Neosalvarsantherapie bei luetischen Erkrankungen des Herzens und der Aorta, Wien. klin. Wchnschr. **33**:77 [Jan. 22] 1920), who review the German literature with reference to this question.

18. Sicard, J. A.: Traitement de la syphilis nerveuse, Presse méd. **28**:281 (May 8) 1920. The French seem to have had a penchant for small dosage, as witness Queyrat and Pinard (How to Cure the Syphilitic, Médicine, Paris **2**:101 [Nov.] 1920; abstr., J. A. M. A. **76**:143 [Jan. 8] 1921). Gougerot (Skin Diseases and Syphilis, Medicine, Paris **2**:85 [Nov.] 1920; abstr., J. A. M. A. **76**:143 [Jan. 8] 1921) states that the larger doses are gaining popularity in early syphilis.

*Osseous Syphilis.*—Arsphenamin deserves a conspicuous place for its promptness of action and the symptomatic relief which it affords in osseous syphilis.[19] Since the Herxheimer reaction is unimportant, administration may be begun at once. Arsphenamin renders iodids unnecessary, as pointed out by Jeans. Cases with delayed response and much suppuration should be searched for sequestrums by roentgen-ray and direct examination; but surgical removal should not be attempted until after some months of intensive treatment.[20] Progressive osseous syphilis of the nose should be searched for epithelioma, and epithelioma in the nose may simulate late syphilis very closely, or be superposed on it. Mercury and arsphenamin administered together in osseous syphilis are more effective than either alone. Osteo-arthritis can be made to involute under treatment, but the Charcot joint when once fully developed, does not respond. No plastic work on bone syphilis should be attempted until after at least a year of intensive treatment, with a negative Wassermann reaction. The coincidence of negative Wassermann reactions with a still active syphilis of the nasal septum is responsible for more than one fallen bridge following operative interference. Hydrarthroses, not frankly of focal or tuberculous origin, should always have a therapeutic test. There is no object in making therapeutic tests on healed osseous lesions.

*Cardiovascular Syphilis.*—Cardiovascular involvement is probably present to some degree in nearly all late syphilis and should be searched for. The presence of obvious signs means a fairly advanced process.[21] The condition of the coronary arteries, difficult to predict from either examination or history, is, I believe, very important. Necropsy experience has made us realize that patients who are seemingly good symptomatic risks may have such a degree of occlusion that death results under treatment from the Herxheimer reaction, or the effects of too rapid healing.[22] Myocardial protest against arsphenamin, even in early cases, can be recognized by transient edema and a dilatation which

19. Jeans, P. C.: The Treatment of Hereditary Syphilis. Description of Method, with Discussion of Results After Four Years' Use, J. A. M. A. **76**:167 (Jan. 15) 1921.

20. For the surgical management of this complication in osteitis of the skull, when it is especially obstinate, compare Adson (The Surgical Treatment of Gummatous Osteitis of the Skull, J. A. M. A. **74**:385 [Feb. 7] 1920).

21. Reid's article is an excellent review of the findings in 105 cases, with a digest of the literature (Specific Aortitis, Boston M. & S. J. **183**:67 [July 15] 1920; cont. **183**:105 [July 22] 1920). Compare also Babcock (Some Practical Considerations with Regard to Syphilitic Aortitis, Am. J. Syph. **4**:34 [Jan.] 1920) and Hoover (Aortitis Syphilitica, J. A. M. A. **74**:226 [Jan. 24] 1920).

22. I have been glad to find that my observations accord with those of Hubert from Romberg's clinic (Footnote 6).

responds to digitalis. Weeks or sometimes even months of mercurial preparation with inunctions and moderate doses of iodids are preferable to the immediate use of arsphenamin.[23] If arsphenamin is used the dosage should be small, and several observers have expressed a decided preference for neo-arsphenamin.[24] In dealing with combined neurosyphilis and cardiovascular syphilis, the cardiovascular lesion is usually the handicap and usually makes intraspinal treatment necessary. Aneurysms too early treated with arsphenamin, may rupture, and a certain amount of symptomatic advance, in the form of developing expansile pulsation[25] sometimes follows too rapid resolution of the mesaortitis and mediastinitis under intensive treatment. Rest in bed affects introspective and hyperactive types unfavorably, but cannot be avoided in threatened or actual decompensation. The anxiety neurosis of these patients is often more serious and obstinate than their syphilis. The patient must be reeducated to a matter-of-fact outlook and a uniform level of activity, without peaks of strain, reduced as the situation may require. At times even an assumed optimism in a consultant transforms the picture. Bromids are a valuable adjunct. Patients with cardiac disorders must be protected from gains in weight. Hypertension with an hypertrophied heart or a well compensated valvular lesion[26] has, as a rule, an excellent tolerance of treatment. Heroic iodid administration in cardiovascular syphilis has no special advantages over smaller dosage that we have been able to recognize.[27]

*Hepatic and Splenic Syphilis.*—A liver palpable just below the costal margin following the first or second arsphenamin injection, with a slight tinging of the sclerae is sometimes all the evidence of diffuse hepatitis recognizable in a given case. Obvious damage to the liver calls for some caution with arsphenamin. On the other hand, the post hoc conclusion that all jaundice following treatment for syphilis is due

23. The various authors mentioned and their citations from the literature show that no unanimity of opinion on this point exists as yet. The value of arsphenamin, used with caution, is generally conceded now. Hirshfelder is a notable exception (Diseases of the Heart and Aorta, Ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 346).

24. Kothny and Müller-Deham (Footnote 17).

25. Hubert (Footnote 6) gives orthodiagraphic evidence of the enlargement of the aneurysm. Goldscheider (Uber die syphilitische Erkrankung der Aorta, Med. Klin. **8**:471, 1912).

26. Hirschfelder (Footnote 23) and Reid (Footnote 21) discuss the fall in blood pressure due to arsphenamin as a contraindication.

27. Hoppe-Seyler: (Die syphilitischen Erkrankungen der Bauch- und der Circulationsorgane [besonders der Leber und der Aorta] und ihr Einfluss auf die Felddienstfähigkeit. Med. Klin. **10**:1727, 1914) advocates iodid given intravenously.

to the medication is unwarranted.[28] The average patient with hepatitis, diffuse or gummatous, tolerates mercury well, and is the better for from two to six weeks of inunctions and iodids, or if much debilitated, mixed treatment by mouth with rest in bed. Only in the very late cases is exhibited the therapeutic paradox [5] of increasing ascites with shrinkage of the liver. In my experience although transient ascites, or an increase of fluid with the Herxheimer reaction, is common, a true therapeutic paradox is rare. When it occurs, and tapping intervals grow progressively shorter, the Talma operation should be resorted to. The good results have been attested by Riesman.[29] The prognosis of hepatic syphilis, if treatment is not pushed too hard, and the patient is not moribund, is good, contrary to the usual belief.[30] Renal irritability is sometimes a serious matter, and demands much attention to foci of infection, diet, and so forth. Amyloid degeneration of the kidney, while a serious complication, does not flatly contraindicate fairly energetic therapy.

In marked splenomegaly the response of the fibrous spleen, in my experience, has not been very good, and when there is accompanying anemia, splenectomy performed by a competent operator yields good results.[31] I have an impression that more effective therapeutic tests on splenomegaly would mean more syphilis recognized and fewer splenectomies performed.[32]

*Gastro-Intestinal Syphilis.*—Gastric symptoms, excluding the frank crises of tabes dorsalis, are present in about one fourth of the cases of late syphilis.[33] If the clinical picture be other than carcinoma, with a positive Wassermann reaction, therapy takes precedence over operation. This is, of course, especially true of hour-glass deformities. But if carcinoma is the probable diagnosis and operability prospects are good, exploration should come first and treatment second, if the findings at exploration confirm the diagnosis of syphilis. Persistence of gastric

28. Syphilitic acute yellow atrophy (toxic hepatitis) is not considered here, since it is an accompaniment of early syphilis. A key to the recent French quasi-polemic writings on this subject can be obtained from Milian (Footnote 8).

29. Riesman, D.: Spontaneous and Operative Cure of Cirrhosis of the Liver. Report of Illustrative Cases. J. A. M. A. **76**:288 (Jan. 29) 1921.

30. Wile (Footnote 5) takes the opposite view; McNeil (Syphilis of the Liver, Am. J. Syph. **1**:738 [Oct.] 1917) agrees with me.

31. A recent complete summary of the status of splenectomy in therapeutics is that of Giffin (Present Status of Splenectomy as a Therapeutic Measure, Minnesota Med. **4**:132 [March] 1921).

32. Eason, J.: The Treatment of Splenomegaly with Anaemia in Syphilitics. Edinburgh M. J. **21**:258 (Nov.) 1918.

33. This is the experience of the Mayo Clinic as summarized by Stokes and Brehmer (Syphilis in Railroad Employees, J. Indust. Hyg. **1**:419 [Jan.] 1920).

symptoms in other than frank crises, after the first few weeks of treatment, calls for further search, in which an astute clinician will often be rewarded with the finding of duodenal ulcer, appendicitis, or other pathologic conditions, slighted or lost sight of when the positive Wassermann reaction was found. Persistent morning nausea, instead of periodic attacks, has in my experience sometimes been a symptom of morphinism complicating gastric crises. In this connection, I cannot refrain from protest at the readiness with which physicians at large prescribe morphin for spasmodic abdominal pain. The tradition has cost lives; for there are few problems more unmanageable than a morphin addict with crises. Arsphenamin is the drug of election in gastric syphilis. The response is one of the most gratifying in the entire field of late syphilis, and seems but rarely dependent on the extent of anatomic change as indicated by the roentgen ray, except in the case of linitis plastica.[34] A gain of 100 pounds in weight occurred in a patient in whom, at necropsy following influenza, a stricture 10 cm. long near the pyloric end of the stomach, was found which would not pass a lead pencil. The starvation acidosis in these cases may need consideration. With involvement of the esophagus and of the rectum, the outlook is proportional to the ratio between active inflammatory infiltration and scar. Patients in the late stages have a poor outlook for medical relief.

*Renal Syphilis.*—Before instituting therapeutic tests for gumma of the kidney one should be reasonably sure that one is not dealing with hypernephroma. Infected kidneys react unfavorably to arsphenamin. Other types of nephritis and nephroses tolerate it much better than mercury, and it may be employed with a phenolsulphonephthalein output of zero without ill effect, provided this low function be not due to urinary retention. Therapeutic tests for syphilitic nephritis are not always infallible, even though the nephritis may respond, at the outset, to some extent to arsphenamin. A nephrosis with a high albuminuria, in the absence of blood and casts and with normal function, may develop late in a vigorous course of treatment.[35]

*Anemia in Syphilis.*—The severe anemias which form a rare complication or accompaniment of late syphilis respond, on the whole, better to arsphenamin than to mercury, although neither is able permanently to influence the course of a pernicious type in the very large

34. Sailer (Linitis Plastica, Am. J. M. Sc. **157**:321 [March] 1916) advises treatment for syphilis when linitis plastica is associated with a positive Wassermann reaction. The occurrence of structural improvement in gastric syphilis has been demonstrated by Eusterman (Syphilis of the Stomach: A Clinical and Roentgenological Study with a Report of Twenty-Three Cases, Am. J. M. Sc. **153**:21 [Jan.] 1917).

35. Lankhout (Syphilis and Kidney Disease, Nederlandsch. Tijdschr. v. Geneesk **2**:2649, 1920; abstr. J. A. M. A. **76**:626 [Feb. 26] 1921).

majority of cases.[36] In fact, I have seen only one case of primary anemia in which the response led me to expect a cure. Avoidance of reactions is highly important. The occurrence of false positive Wassermann reactions in primary anemias has led to more than one disappointing therapeutic test. Anemias of secondary type, of great persistence, largely uninfluenced or at most only temporarily influenced by any form of treatment, occur in late syphilis. One that I recall responded to removal of a septic gallbladder.

Wassermann-resistant patients,[37] instead of being dismissed with reassurances, need, I believe, intensive study and lifelong observation. Paradoxically, however, I do not believe the reversal of the Wassermann reaction to be an end in itself, since its relation to the structural or functional integrity of any organ is as yet obscure. As one's experience with modern therapy increases, fixed positive reactions become fewer, especially following the prolonged use of inunctions. The Pollitzer technic is especially extolled [38] as a means of reversing resistant cases, but should only be used after a comprehensive survey of the case. Other conditions besides paresis may underlie an irreversible test. The reputed resistant Wassermann reaction in children has not materialized in either Jeans' [19] experience or my own. I have seen nothing to confirm Strickler's [39] impressions as to the influence of arsphenamin in the production of false or persistent positives.[40]

*Syphilis of the Eye.*—I am returning to Ehrlich's original belief that arsphenamin is distinctly contraindicated in some cases of simple primary optic atrophy (not secondary to neuroretinitis or choked disk), at least in the early months of the course. I have seen a patient with good vision go totally blind with four arsphenamin injections, and another, with primary optic atrophy, due to high myopia, have to be transferred to mercury because of its action. On the other hand, focal infections in the mouth, stirred up by mercury, occasionally cause trouble from the other direction. Treatment for syphilis, especially with arsphenamin and the iodids, has marked nonspecific effects in the eye,

36. Gorke (Auftreton von apastischer Anämie nach Salvarsan, München. med. Wchnschr. **67**:1226, 1920). Compare also Footnote 9.

37. Footnote 13. Compare also Wile, W. J., and Hasley, C. K.: Serologic Cure (?) in the Light of Increasingly Sensitive Wassermann Tests, J. A. M. A. **72**:1526 (May 24) 1919.

38. Footnote 16, first reference.

39. Strickler, A., Munson, H. G., and Sidlick, D. M.: A Positive Wassermann Test in Non-syphilitic Patients After Intravenous Therapy, J. A. M. A. **75**:1488 (Nov. 27) 1920.

40. For a critical consideration of the merits of this question, compare Kolmer, J. A.: The Question of Positive Wassermann Reactions Caused by the Intravenous Administration of Arsphenamin, correspondence, J. A. M. A. **75**:1796 (Dec. 25) 1920.

which could be more widely utilized in the treatment of uveitis, episcleritis, tuberculous keratitis, and so forth. Ophthalmologists are all too unfamiliar with the effect of arsphenamin on intestitial keratitis, which is an immense advance over the effect of mercury, although it must be combined with it for permanence. The value of months and years of persistence in seemingly hopelessly impaired cases has been impressed on me.

*Syphilis of the Ear.*—Deafness in hereditary or acquired syphilis should always be intensively treated, regardless of its duration. The occasional patient exhibits unexpected improvement (test it by speaking from behind the patient to keep him from reading lips). In acute onsets I prefer mercurial preparation, but I have seen no ill effects from arsphenamin. Patients with associated neurosyphilis may make an especially good response. Patients with positive Bárány reactions may make some objective improvement, but I believe the specificity of this response is still open to question.

*Syphilis of the Nose and Throat.*—The response to arsphenamin is miraculous and sometimese life-saving, when deglutition has been obstructed, but if the process involves the larynx or trachea, the immediate use of this drug, even in seemingly trivial lesions, is dangerous because of the Herxheimer reaction. Provocative procedures must not be used in such cases. On the tongue, the coincidence of lesions undergoing malignant changes and new crops of recurrences is possible. I have seen hemiglossectomy performed for carcinoma on gumma, while later, because no treatment was given for the syphilis, another gumma was allowed to develop and degenerate on the other side. The confusion of the pathology of gumma with that of tuberculosis of the tongue (so-called "tuberculoma") with a positive Wassermann reaction is more common perhaps than is realized.

### SYPHILIS IN MOTHER AND CHILD

Syphilis in the mother [41] is one of the richest fields for prophylactic effort now available, as indicated by the steady influx of favorable reports of the work of obstetric services and prenatal care clinics,[42]

41. Skinner (Syphilis at a Venereal Clinic: An Analysis of Cases Admitted During Twelve Months, Lancet **1**:650 [March 20] 1920) points out, however, how few women report for examination or treatment short of a fully developed infection.

42. Williams (The Significance of Syphilis in Prenatal Care and in the Causation of Foetal Death, Bull. Johns Hopkins Hosp. **31**:141 [March] 1920) found 53 per cent. syphilitic children of untreated mothers, 7.4 per cent. of mothers treated during pregnancy. Compare also Adams, J.: Treatment of Ante-Natal and Post-Natal Syphilis, Brit. M. J. **2**:541 (Nov. 16) 1918; and Chambrelent: La mortinatalite en France. Elle est evitable dans la majorité des cas, Nourrison **8**:321, 1920.

in which the problem is beginning to receive the attention it deserves. Syphilis in the child should receive the same treatment as syphilis in the adult, in response to a growing appreciation that apart from stigmatization and the high mortality of untreated uterine infections, it presents no essential differences. In fact, the surviving untreated child has a resistance that is a valuable asset in treatment. Instead of boring you with a recital of technical details, let me summarize what I conceive to be essential principles. The relative immunity of the woman from external manifestations of the disease and the suppressing effect of pregnancy and lactation has placed syphilis in women in a field by itself. The institution of therapy for the protection of the child seems to me justified in women in whom evidence of syphilitic infection is so doubtful that the advisability of treatment would be questionable under other circumstances. The studies of Widakowich [43] on spermatozoal anomalies and the findings of Eberson [3] in the male syphilitic furnish the first tangible hint of direct paternal influence [44] and raise the question of whether or not the father should have treatment as a preparation for conception quite as much as the mother for gestation. This constitutes what I have both preached and practiced as "treatment for life insurance" in the parents of a syphilitic child. Of late I have grown almost radical enough to believe that at no time can the woman who has had syphilis be advised to go through pregnancy without a treatment course coincidently. While this would bear hard on the mother of nineteen children, it need not be a hardship to the average family, and might, if observation of the children thus born should justify it, permit a relaxation of rules with respect to marriage.

Spirillicidal methods must be a prominent feature of the treatment of the pregnant woman, since a maximum destruction of organisms is, at least so far as our present knowledge goes, the best protection to the child. There seem to me to be good reasons for giving from one half to two thirds of the full doses all around, to the pregnant woman. Her infection is to some extent inhibited by her pregnancy,[45] her liver and kidneys are both under strain, as evidenced by the familiar intoxi-

43. Widakowich, V.: The Spermatozoa of Syphilitics, Semana med. **27**:633 (Nov. 11) 1920; abstr. J. A. M. A. **76**:414 (Feb. 5) 1921.

44. Routh (Antenatal Syphilis: Suggested Action of the Chorionic Ferments, abstr. Brit. M. J. **1**:47 [Jan. 12] 1918) makes an interesting argument for a paternal factor on the basis of Noguchi's spirillolysis, attempting also to explain delayed infection of the fetus in untreated cases.

45. Brown, W. H., and Pearce, Louise: On the Reaction of Pregnant and Lactating Females to Inoculation with Treponema Pallidum—A Preliminary Note. Am. J. Syph. **4**:593 (Oct.) 1920.

cations of pregnancy, and her metabolic and eliminative mechanism therefore cannot be equal to massive treatment.[46]

Whether the child born symptomless will remain so, is the crux of the prophylactic phase of treatment in mother and child.[47] The possibility of long periods of latency after birth in children treated during uterine life, familiar in the untreated infection as well, demands the fullest development of facilities for the following up and observation of the syphilitic family before the cure of the child by treatment of the mother is accepted as established.

Systems of treating the child show a commendable trend toward increasing intensity, tempered by the realization that most uterine syphilis is late syphilis.[48] Fordyce and Rosen's [49] advocacy of intramuscular arsphenamin is intended apparently to popularize the drug with those technically inexperienced.[50] I agree with Jeans [19] that the expert seldom or never has need to use other than the intravenous route.[51] The tolerance of children for mercury is proportionately greater, I believe, than that of adults, and the intramuscular and inunction routes are gaining a well-deserved popularity. As a relief from the debilitating effects of prolonged mercurialization, arsphenamin is even more welcome in the treatment of children than in that of adults. The synergistic effect of the two drugs is also valuable in obstinate cases. Intraspinal measures have been effectively used.

The conception of the Weylander school-hospital for the combined treatment and education of children with heredosyphilis has not received the attention it should have in this country. The reports from the Scandinavian countries and Germany indicate that it solves the problems of hospital care and social rehabilitation.

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46. Adams (Footnote 42, second reference) praises liberal doses of arsphenamin for mothers, but his mercurialization is practically all by mouth. Williams (Footnote 42, first reference) does not specify his technic, but it seems to have been conservative.

47. Much rather unguarded emphasis is being placed on the child's negative Wassermann test after birth.

48. Veeder, B. S., and Jeans, P. C.: The Diagnosis and Treatment of "Late" Hereditary Syphilis. Am. J. Dis. Child. **8**:283 (Oct.) 1914.

49. Fordyce, J. A., and Rosen, I.: A Method of Treating Congenital Syphilis. J. A. M. A. **75**:1385 (Nov. 20) 1920.

50. Adams (Footnote 42, second reference) commends galyl in glucose, one seventeenth of the adult dose.

51. It would be interesting to apply the proportionally huge doses of neoarsphenamin by rectum, employed by Mehrtens (Rectal Injections of Massive Doses of Neo-Arsphenamin, J. A. M. A. **76**:574 [Feb. 26] 1921).

## CONCLUSIONS

This rather cursory review of the principles underlying certain special phases of syphilis will defeat its own purpose if it leaves the impression that the treatment of the disease should be parceled out in segments, each self-sufficient and governed by its own laws. Just as we are finding that early syphilis is no longer localized, even at the earliest appearance of the primary lesion, so we shall find as the intensity of our study increases that late syphilis does not begin in the first decade, but in the first hour. Preventing the transmission of the disease in its earlier stages, and forestalling the individual tendency to complications based on the peculiarities of the strain of parasite, the host, and the method of treatment, is the whole problem of syphilis. Forestalling implies detection, so that an increasing diagnostic alertness, a development of methods for detecting the earliest and not the late signs of pathologic change in vital organs and tissues, is not mere diagnosis, but a part of effective treatment. For all our so-called prophylactic effort, nothing will prevent the development of late complications in a certain group of patients who present the fatal combination of predisposed soil and tropic organism. It is equally true that an even smaller group of patients will master the infection for themselves, irrespective of our interference. Between these two extremes will come those whom we have radically cured, those whom we have managed to place in commensal relation to their infecting organism, those whose immunity we have broken by treatment measures whose potentialities for future harm as well as present good we do not yet understand, and those whom we have destroyed outright by treatment itself. The study of the interrelation of these groups is one of the most complex problems of the medicine of today. Its solution will not be accomplished by a mental or a physical separation of the various phases of syphilis and syphilotherapy into air-tight compartments each with its own technic, ideals and aims. Only that mode of approach will leave a significant impress on our future knowledge which envisages the entire disease, employs one or two methods in a large series of cases over a period of many years, records the results, and which, by lifelong observation and periodic complete reexamination, detects impending serious pathologic change, and evaluates in detail and with accuracy the response of parasite and host.