I

THE INTERPRETATION AND MANAGEMENT OF LATENCY IN SYPHILIS

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THE steady retreat of the syphilitic infection into invisibility under the action of symptom-obliterating, though not necessarily curative, drugs, and medicine's equally determined pursuit of its faintest traces by more and more searching tests, has created in the past two decades a situation of unusual interest, and one still far from evaluation so far as the welfare and outlook of the patient is concerned. The conception of latency in syphilis is an old one, based upon the superficial and symptomatic syphilology of the nineteenth century rather than the immunology, pathologic physiology, and serology of the twentieth. Its basic notion of a still existent but completely symptomless infection becomes increasingly tenuous as the comb with which we search the medical background of the seemingly well person develops finer and finer teeth. Asymptomatic yet existent syphilis becomes rarer as we identify, by routine testing of all patients, for example, the positive blood Wassermann reaction; the chicken-track pigmentation at the periphery of the ocular fundus for which none but the ophthalmologist, and too often not even he, was looking a few years ago; the accentuated aortic second sound; the exaggerated pulsation and expansion of the aortic arch observed with the fluoroscope; and the undoubted but cleverly concealed symptom of the abnormal spinal fluid in the total absence of neurologic signs. Symptomless syphilis, like mono-symptomatic syphilis, tends to become the rarer the more careful our search of the supposed carrier of the disease.

A redefinition of latency in syphilis is, then, in order. To base such a definition merely upon absence of symptoms, or upon a mono-symptomatic criterion such as

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the positive blood Wassermann reaction, lays us open to a perpetuation of old misconceptions and to early reversal at the hands of better and better methods of examination. It would seem to be more contributory to rationalisation of both diagnosis and treatment to base the definition of latency upon pathologic physiology and immunology.

The older chronologic syphilology placed the period of latency vaguely between the disappearance of secondary syphilitic lesions and the onset of tertiary syphilis. It recognised the development of resistance to the disease spontaneously or by treatment. It recognised, but did not place sufficient emphasis upon, relapse and recurrence, nor draw the important distinction between a group of cyclical surface phenomena and a group of steadily progressive parenchymatous degenerations. Both these conceptions are essential to the appreciation of the pathologic physiology of latency to-day. Latency in syphilis may now best be described, not as an asymptomatic lull preparatory to destructive late manifestations, but as a period of high resistance and low visibility, with an undercurrent of chronic mild inflammatory change in vital structures and an upper stratum of alternating relapse and recovery. To our appreciation of the former aspect the American investigator, Warthin, has been one of the most fundamental contributors, and to our comprehension of the relapse cycle, Brown and Pearce, of the Rockefeller Institute.

What is called latency, then, in spite of its few clinical manifestations, is not a state of inactivity or quiescence, except in the occasional rare case of a perfect symbiosis of host and *Spirochæta pallida*. The latent stage is rather a busy period of microscopic change in innumerable foci, many of them quite inaccessible to clinical study until after "something happens." The long periods in which the unruffled surface of the patient's physical life presents no evidence of the disease are the products of a relative immunity, maintained by slow, chronic inflammatory changes, especially in the parenchymatous structures and the vascular system. The unit in this type of defence is the group of lymphocytes and plasma cells which collects as an irritative reaction about the spirochætes lying in the lymph spaces surrounding the minute vessels. The reaction set up in the vessel in the form of endarteritis

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reduces the blood supply of part of the parenchyma, with ensuing degeneration. The lymphocytic infiltration, following identically the course of the typical tissue reaction at all stages of the disease, is gradually replaced by fibrous tissue, and a further loss of parenchyma occurs. The end-result of this resistance-maintaining focal reaction is, therefore, *degenerative*, and replacement of a functionally active tissue by an inert and weakened scar takes place. These individual reaction units are almost infinitely numerous. Their slow, combined action *ages the patient* by the induction of premature fibrosis, and threatens the integrity and impairs the functional capacity of his vital structures by destroying their very substance and replacing it with connective tissue.

While in this rather costly fashion the outward freedom of the patient from gross signs of the disease is being maintained for a period, local foci from time to time, following the typical cycle of infection—reproduction of organisms, reaction of tissues, suppression of organisms and relapse—break through the mask of latency with redistributions of spirochætes *viâ* the blood stream, and with slight but none the less real evidences of activity. These include, for example, transient anæmias, loss of weight, periosteal infiltrations, cutaneous and mucosal recurrences, and those instances of isolated syphilitic pregnancy in a series of healthy children which were such puzzles to the older generation of clinicians. Nor must it be imagined that the interest of the internal degenerative mechanism of latency for the practitioner is purely theoretic. When these changes develop, as they so commonly do, in the wall of the aorta, fibrous tissue replaces elastic tissue and the bulge of an aneurysm results. Hæmorrhages, thromboses, and ischæmias in the nervous system, the myocardium and the coronaries, cirrhosis in the liver, and in fact much the larger part of what we know as clinical late syphilis, has its stage set in the seemingly innocuous period of latency. The patient who has a latent infection is *living on his parenchymatous capital*, and his life will be long or short, happy or calamitous, in direct proportion to the balance which his body, with its inflammatory-degenerative defence mechanism, is able to maintain against the activity of his ubiquitous spirochætal enemy.

The renascence of the conception of the defence

mechanism in latency has become one of the most important issues in the whole field of syphilology, and the stamping ground for unsolved questions, over and under-emphasis, and misconceptions almost overnight. If we accept the positive blood Wassermann reaction, in the absence of other symptoms, as defining a latent syphilitic infection, it may be contended that a positive Wassermann is an immunity reaction most frequently observed in that group of syphilitic infections which involves the so-called protective structures, such as the large viscera, the bones, and the skin. It may be reasoned that because these tissues appear by their reaction to protect at least the nervous system from involvement the positive Wassermann reaction is a veritable beneficence, and not to be lightly attacked, lest by reversing or suppressing it the patient may be actually robbed of his immunity. On the other hand, it is an undoubted fact that syphilis may be progressive to a fatal result with a negative Wassermann, and that it requires only an increasing sensitiveness of technic to demonstrate a positive Wassermann in many who, having had syphilis, are negative to the ordinary technics. One may, then, resign himself to the horns of the dilemma by denying that either the positive or the negative blood Wassermann reaction has any bearing on the arrest or activity of a syphilitic infection, and that latency defined in terms of a Wassermann reaction alone cannot, therefore, have any significance for the patient. Personally I am inclined, with reservations, to align myself with this latter point of view and to oppose the definition of latency by the Wassermann reaction. I hesitate to draw conclusions as to the progressive or innocuous character of a given syphilitic infection from the results of a blood test. My personal experiential basis for this stand lies in the clinical study of the fixed or resistant positive blood Wassermann reaction, on the one hand, in which Busman and I found that cardio-vascular and parietic neurosyphilis, often well below the threshold of clinical recognition for years, were too often the complications that brought the Wassermann-positive, seemingly latent patient to book; and the studies of Des Brisay and myself on the serologic findings of untreated syphilitic patients, in which it appeared that Wassermann-negative latency more frequently resolves itself into neurosyphilis

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of other than paretic types than into any other manifestation of the disease. In fact, all the statistical surveys made from the syphilologic material of the Mayo Clinic between 1916 and 1924 distinctly indicated that a pronouncement of latency or cure based on a negative blood Wassermann reaction in late syphilis runs afoul of neurosyphilis and the abnormal spinal fluid more often than anything else. No less than 30 per cent., and often as high as 60 per cent., of the neurosyphilis which passes through a general diagnostic clinic will be dismissed as non-syphilitic if only the blood Wassermann test be employed to determine its existence. In a study by Brown and myself of 200 syphilitic patients whose chief complaint was stomach trouble, it appeared that only 44 per cent. had positive blood Wassermann reactions, while 59 per cent. had abnormal spinal fluids, and 75 per cent. had neurosyphilis. Seventy per cent. of the patients who had persistently negative blood Wassermann reactions not due to treatment had positive findings in the spinal fluid. Of 200 patients with syphilitic cardiovascular disease, 40 per cent. had negative blood Wassermann reactions on first examination. Elliott places the margin of error of the negative blood Wassermann reaction in this aspect of the disease at the same figure ; Reid at 17 per cent. ; Cummer and Dexter at 25 per cent. ; Longcope at 75 to 12 per cent., depending on the aspect under consideration. If, then, neurosyphilis in general shows a distinct trend toward blood Wassermann negativity, and the most persistently positive blood Wassermann reactions on searching investigation or prolonged observation resolve themselves into aortitis and paresis, what possible reliance can be placed on the blood Wassermann reaction in any of its moods for the definition, status, and life expectancy of the patient with so-called latent syphilis ?

Once we thus rid ourselves of a Wassermann-bound concept of latency we become free to inquire further as to its definition and the therapeutic requirements, if any, of the latent period. The definition of latency in syphilis depends upon a combination of complete examination and lifelong repeated observation. To accept the blood Wassermann report as a complete account of the status of the infection is impossible to any one with more than a rudimentary experience with the disease. It must be

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obvious that the definition of Wassermann-negative latency depends upon the spinal fluid examination and the physical and neurological examination, to say nothing of the special examinations of the eye, the eighth nerve, etc.

If so much can be said for the failure to investigate a negative Wassermann, much more might be said for the all too frequent failure to inquire into what lies back of a positive. Present-day syphilologic consultation seems almost at times to consist largely of insistence that the physician who has been treating his patient with a positive blood test in a desultory fashion for years, or who has all but dismissed him from his office with a single positive test, but no symptoms, shall have that patient's spinal fluid examined. As a classical example of the disastrous habit of minimising a positive blood Wassermann reaction, the following case memorandum is offered, because the patient and his advisers were not mere labourer and country doctors, but the cream, the upper crust, of the business and medical professional world :—

MINIMISING A POSITIVE WASSERMANN

- 5-4-19. Came complaining of backache. Sacro-iliac X-ray negative. Focal infection suspected, but Wassermann positive. Gonorrhœa twice, but no history of syphilis.
 - 5-6-19. Wassermann repeated with same result, persistently positive.
 - 5-7-19. Seen by syphilologist, sent to neurologist.
 - 5-9-19. Neurologic examination negative.
 - 5-10-19. Returns home to consider next step.
 - 5-23-19. Returns to clinic and has another Wassermann. Result positive.
 - 5-25-19. Calls on syphilologist informally and is advised to have spinal fluid examined. Declines, saying that several noted physicians have told him that his blood-tests are nothing serious, and treatment is unnecessary. Is warned that his examination has been inadequate.
 - 7-9-19. Has an attack of unconsciousness lasting two and a half hours. Assured that it is "heat stroke," but cannot forget his positive Wassermann.
 - 7-19-19. Returns to syphilologist for reconsideration.
- Cerebrospinal Fluid :*
 W.R. : +++ ; Nonne, positive ; lymphocytes, 161 ; Colloidal gold, 0112322100.
 Prolonged and intensive treatment has been without effect other than to reduce the pleocytosis.

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ALWAYS ASK YOURSELF WHAT LIES BACK OF A POSITIVE WASSERMANN

It follows, then, that it should be a first principle of modern syphilologic practice to examine the spinal fluid of all patients who are known to have, or who have had, syphilis at the earliest possible moment, barring the first few weeks of treatment for an early infection. The same principle applies to patients against whom a reasonable suspicion can be made to rest, even though their blood Wassermann reactions are repeatedly negative both direct and to provocative procedure. A negative neurological examination is by no means to be accepted as a substitute for the spinal fluid examination, for it deals only with the scars and residua of a well-established process, and not with its preventable and controllable beginnings. It is the hesitation of the practising physician who regards the spinal fluid examination as a species of ordeal or trial by fire rather than as the safe, painless, and usually reactionless procedure which it is when properly performed and controlled, that at the present time permits so much easily recognised and accurately definable serious syphilis to slip through to irreparable consequences under the guise of a spurious latency.

To give greater concreteness to my suggestion that Wassermann-positive latency resolves itself not infrequently into cardiovascular syphilis, I append, with their discussions, two case summaries which illustrate, from my teaching material, a considerable group in whom the detection of the most serious aspect of their disease followed the routinisation of complete examination in patients whose status and early treatment had been determined chiefly by the incomplete evidence of their positive blood Wassermann reaction :—

THE OVERLOOKING OF CARDIOVASCULAR SYPHILIS IN A MULTIPLICITY OF OTHER COMPLAINTS. PRESENTING SYMPTOMS OF NEURO- SYPHILIS. CARDIOVASCULAR SYPHILIS UNDERLYING A FIXED POSITIVE BLOOD WASSERMANN REACTION.

Housewife, age fifty-three years.

<i>Examined</i> March 25, 1920.	<i>Appendix</i> troublesome for years,
<i>Chief Complaint</i> : Left eye turns	removed in 1916.
in.	"Sore bladder and kidneys" next.
<i>History</i> : Two healthy children	<i>Food poisoning.</i>
followed by two miscarriages.	<i>Teeth pulled.</i> Hæmorrhage later.

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Uterine curettage. Felt good for a while.
Neuralgic seizures in head.
"Pain in teeth," though teeth were out.
Pains in legs, "neuritis," several years.
Loose cartilage in knee for twelve years.
Unconscious seizures for one and one-half days. Slight fever.
Profuse discharge of pus from nose.
Diplopia developed one week later. Left eye turned in. Patient came to clinic.
Examination: Paralysis of left internal rectus.
 Tonsils negative.
 Teeth all out.
 Antrum X-ray, cloudy right. Frontal sinus also.
 Nose "suggests possible syphilis."
 Blood-pressure, 140/75.
 Heart, short blowing systolic murmur.
 Tambour aortic second sound.
 Edge of liver palpable.
 Some tenderness in lower abdomen.

Neurologic Examination: Meningeal neurosyphilis.
Spinal Fluid: Wassermann+++ 0.4 c.c.
 Nonne positive, 20 lymphocytes.
 Gold sol 0122222211. Later a first zone gold sol appeared.
Blood Wassermann Reaction: Strongly positive.
Diagnosis: Cerebrospinal syphilis. Right accessory sinus infection.
Treatment: Three courses of arsenphenamin, three courses mercury succinimid, 132 inunctions.
Symptomatically the Patient was transformed.
The Spinal Fluid became Permanently Normal after the first year.
Blood Wassermann Reaction persistently positive during three years of observation.
A Special Cardiovascular Examination then asked for in the effort to explain the fixed positive, gave proper weight to the vascular findings that had been overlooked.

DISCUSSION

1. *The cartload of symptoms laid at the door of the first inquirer naturally obscures the picture.* The first item on which he can focus his attention is the rectus paralysis, and this is promptly run to earth with the assistance of the Wassermann and spinal fluid tests and the neurologic examination.
2. *The aortic murmur, however, being for the moment outside the focus of attention, is heard but not interpreted,* in the blanket designation of "syphilis" applied to the whole case. The same applies to the moderate hypertension and the "tambour" aortic second sound.
3. *Note also the liver, which escaped consideration in the summary.* The nose, suspected of being syphilitic, cleared up under treatment.
4. *The syphilologist likewise proceeded to treat on the basis of the presenting lead, the neurosyphilis.* It is not until a persistent positive blood Wassermann reaction is encountered, with a ready response of the spinal fluid, that he begins a search for some explanation of the paradox.
5. *The resistant positive blood Wassermann in a late case* is as suggestive of vascular as of neural pathology.
6. *Asymptomatic aortic syphilis demands for its clinical recognition concentrated attention* to the physical signs, and particularly to the

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aortic systolic murmur and the accentuated aortic second sound with mild hypertension. Had this woman not had neurosyphilis, she might not even have had a Wassermann test, supposing she had emphasised some one of her other complaints. She recalled, on questioning, some dyspnoea and nocturnal precordial pain for several years.

EARLY DIAGNOSIS OF AORTIC SYPHILIS CONFIRMED BY SUBSEQUENT OBSERVATION. ACCENTUATION OF SIGNS UNDER TREATMENT WITH PROGRESSION OF LESION. IMPORTANCE OF CARDIOVASCULAR STUDY IN THE FIXED POSITIVE BLOOD WASSERMANN CASE.

Business man, age forty-five years, married.

Examined August 21, 1919.

Chief Complaint: Stomach trouble. Vomiting after meals, emaciation. Five months' duration.

No History of Syphilis: several attacks of gonorrhoea. Wife and three children well.

Left Testicle Removed for "Sarcoma" a year before present examination.

General Examination: Negative, including X-ray of the stomach. Blood-pressure 118/70; heart negative. Achlorhydia.

Blood Wassermann Reaction: Strongly positive, repeatedly.

Consultant's Note: "Stomach and testicle both syphilitic" (?)

Treatment: Six injections arsphenamin, 15 mercury succinimid, 35 inunctions.

Spinal Fluid: Negative.

Wife's Blood Wassermann Reaction: Strongly positive.

Children: Three, one with peripheral choroiditis, Wassermann reaction negative on the blood.

On Return for Observation after above Treatment, greatly improved, but Blood Wassermann Reaction still strongly positive.

Because of this Blood Finding he was sent for a special cardiovascular study by Willius.

Cardiovascular Examination (Willius):

No cardiovascular symptoms. Heart 4 by 9.5 cm. No arrhythmia.

Second sound at base accentuated, especially at the aortic area where the sound accentuation is almost rasping in character. This suggests a rigidity of the aorta indicative of peri-aortitis. No murmurs heard.

Blood-pressure 130/76. Pulse 60.

X-ray of chest negative.

Electrocardiogram: Rate 53, sinus bradycardia, left ventricular preponderance.

Diagnosis: Probably early peri-aortitis, syphilitic.

Treatment: Second course of 6 arsphenamin injections, 20 mercury succinimid, 32 inunctions.

Cardiovascular Re-examination: Nine months after the above. No complaints or change in symptoms. Blood-pressure 138/72. *Diagnosis* peri-aortitis.

Blood Wassermann Reaction: still strongly positive.

Treatment: Third course of 6 injections of arsphenamin, 18 mercury succinimid; 24 injections mercury salicylate at home.

Returned after Three Years' Absence: Felt in best of health and condition. No complaints.

Cardiovascular Re-examination (Willius): No complaints.

Heart dulness 4 by 10 cm. No arrhythmia. Systolic murmur at aortic area.

Diastolic blow also heard with

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point of maximal intensity to left of midsternum.	Sinus bradycardia. Inverted P wave III, Inverted T wave
Capillary and water-hammer pulse.	III, left ventricular prepon- derance.
Blood-pressure 162/80, pulse 80.	Diagnosis: Syphilitic aortitis and
Electrocardiogram: Rate 60.	aortic regurgitation.

DISCUSSION

1. *Note that at the time this patient presented himself he showed no sign and has never made any complaint which would serve to identify the most serious aspect of his medical condition. Note that his wife had a positive blood Wassermann reaction. Note that though the children's blood Wassermanns were negative, one of them had a peripheral choroiditis.*

2. *The investigation of the patient's cardiovascular system was inspired by the fact that he had a resistant positive blood Wassermann reaction. His chief complaint of stomach trouble, associated in this case with an achlorhydia and not with neurosyphilis, was promptly relieved by treatment.*

3. *The examination of the cardiovascular system disclosed an accentuated aortic second sound "almost rasping in character," interpreted as suggestive of rigidity due to peri-aortitis.*

4. *This cardiovascular examination was made after the patient had been under treatment six months. Does it then represent the progress of a lesion not previously detectable, in spite of treatment, or sclerosis of the aorta either as a result of involution of a peri-aortitis or from the toxic action of the medication?*

5. *Of these possibilities it seems to me the more probable that we are dealing with a sclerosis associated with healing rather than a lesion newly developed in spite of treatment.*

6. *During a subsequent nine months, while the patient was under efficient treatment, the lesion showed no progress.*

7. *Subsequently, however, all the signs of aortic regurgitation developed.*

The Relation of Spurious Latency to Treatment.—The consultant is occasionally asked why it should be a matter of such moment to determine in detail, and in advance of treatment, the status of the patient with a positive blood Wassermann reaction. "He has syphilis—why not simply treat him?" is the question not infrequently asked. If treatment were a matter of routine and uniform procedure, regardless of the clinical type of involvement, the full investigation of the seemingly latent case might well await a better personal acquaintance with the patient. But the demands of individualisation are becoming so insistent, and the treatment, for example, of an early cardiovascular or hepatic syphilis so different from an osteitis of the skull, that an appraisal of the situation is *sine qua non* to intelligent management.

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The nervous and the vascular systems more often perhaps than other structures suffer severe shock, and often lasting damage, from the brusque application of arsphenamine therapy, which would be appropriate enough in a patient with no discoverable lesion other than a positive blood Wassermann test. Complete examination is, then, a fundamental preliminary of treatment decisions of every type involving a genuine or a spurious latency.

Having now attempted the definition of latency by suggesting that it becomes a comparative rarity when proper methods of examination and observation are applied, it is in order to consider from the standpoint of treatment the case of the patient who may be said to be in a state of serologic latency, or Wassermann-positiveness without any other sign of the disease discoverable on painstaking and complete examination. In this connection it is well to recall the general aim of treatment for syphilis—the prevention of transmission of the disease and the insurance to the patient of a long life free from complications and disabilities traceable to it. It is not the reversal of the blood Wassermann reaction or the reduction of an abnormal spinal fluid to normal *per se*. It is not the removal or restoration of residua if they inflict no disability. It is not even the extinction of the last spirochæte, if the last spirochæte is completely encapsulated and harmless. Reflection upon these ideals will occasionally temper a therapeutic furor or restore a perspective which has become a trifle distorted by too much study of paper findings, laboratory reports, and records. The “squirrel-in-a-cage” frame of mind into which one is occasionally driven by the persistence, resistance, and relapse that characterise clinical syphilis in consultant practice is often wonderfully relieved and refreshed by occasional proof that if arsphenamin and mercury won’t control syphilis, common sense and a rest period perhaps will. The collateral factors of treatment embody the amenities, the reliefs, the good news, the kindly and balanced judgments, and the human considerations of syphilologic practice.

Appraisal of Resistance.—It is easy for the amiably disposed physician to say, “You look pretty well—I guess you don’t need treatment.” Yet he should never pass this welcome judgment upon his patient without giving genuine pause to consider the actual meaning of

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his words as applied to the specific case. The decision to place a patient upon his own resistance or to leave him to his defence mechanism is a momentous one, never to be lightly made. As we have seen, it is difficult to make more than a speculative estimate of the state of the defence even after careful examination. Freedom from symptoms to-day may be succeeded by diplopia, paraplegia, apoplexy, death from coronary thrombosis, to-morrow.

Granted, then, the thoroughness of the examination, we may say that if no active lesion be found, if the latency can be pronounced genuine, the evidence of the disease confined to scars of extinct processes or to a repeatedly positive blood Wassermann reaction, then, and then only, may we raise the question as to whether it is better not to treat than to treat. In the presence of an obviously active lesion, of an early syphilis which is transmissible or of a latent one which may become so, the decision to treat is medically, and often morally, obligatory. If the patient has had a little modern treatment, but not enough, the cardiovascular and nervous systems deserve special study, for it is precisely here that the inadequately treated patient most often carries his concealed death warrant. The syphilitic mother is a candidate for treatment under all circumstances, unless she be beyond the child-bearing age or instructed as to contraconception. Infections which were virulent and outspoken in their earlier cutaneous manifestations, or in involvements of the grosser defence mechanism, such as the bones and the liver, are less likely to show degenerative lesions than are those with a practically negative history. The establishing of a complete base-line investigation, including a neurological study in every latent case, at first consideration makes possible the invaluable later re-checkings, which alone can show the ultimate meaning, short of autopsy, of the positive blood test. Marital history is important, and the occurrence of a neurosyphilis or cardiovascular syphilis in one member of a couple, the other one having a positive blood Wassermann, demands a full study of the possibilities of the all too frequent conjugal involvement. Thus the wife of a tabetic or paretic should always have a neurological and a spinal fluid examination if there is any likelihood of infection.

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The Decision to withhold Treatment.—The decision not to treat a latent syphilis should stand out clearly in the mind of a physician as a placing of the patient upon his unaided resistance mechanism. It is for the moment a somewhat uncritical fad among conservatives to advocate even the placing of the early syphilitic infection upon the resistance or defence mechanism by withholding treatment, or in preference to the use of modern arsenicals. Conservation of the defence mechanism in latent syphilis is certainly of vital importance, and it sometimes demands the avoidance of large doses of the arsphenamines. But in general, as Des Brisay and I found in a survey of 413 cases, 208 of them previously unrecognised and untreated, the efficiency of the unaided defence had brought about less than 1 per cent. of spontaneous arrest. It would certainly seem that the decision to place the patient on his defence mechanism must have other background than this to justify withholding treatment from the latent case. This modifying background is found in the age and time factors in the individual case.

Age and Time Factors in the Treatment of Latency.—In answering the question as to how much the patient with latent syphilis can depend on his resistance, and how much resistance he will need to attain the best possible life-result, age and time factors are of the greatest importance. They are important from the standpoint of the social order as well as the individual. It is all too easy to think of them only in terms of the patient, and not in terms of his possible contacts and future activities. While a syphilitic infection does not, of course, as I have said, travel at a uniform rate towards a definite goal, it is possible to generalise to some extent on the progress which it will be likely to make toward serious degenerations and crippling damage in a period of years. Thus an infection of long standing, say twenty to forty years, in a patient of fifty to seventy years of age, provided no serious signs of activity can be discovered, demands little or no treatment. The long duration has, in the vast majority of cases, done away with risk of infecting others, so that the responsibility of the physician for the control of a possible carrier has been discharged by time. A patient over fifty years old with such a slowly progressive or clinically stationary infection will come to his death from other causes before his syphilis gives rise to serious

degenerations. He may be left to the care of his defence mechanism. On the other hand, a patient between fifty and seventy who acquires a fresh infection thereupon assumes the status of a carrier, and the social demand for protection from him takes precedence over any question of what may be best suited to his age and physical make-up. Unless there are very positive contra-indications—and there seldom are—an old man should receive the same sterilising treatment as a young one. Our experience has tended to show that age is not, as such, a contra-indication to effective abortive treatment for syphilis.

Latency in Age Thirty to Forty.—On the other hand, the time relations change with the patient in his thirties or forties. At this age he will have abundant time to use up all that could reasonably be expected of his immunity mechanism. He may thus be left still in his years of presumably high effectiveness crippled by some late degeneration. Even though there may be no symptoms except a positive blood Wassermann, and sometimes even during Wassermann-negative, asymptomatic latency, he should receive effective treatment for the disease. It is indeed an exceedingly serious matter for a patient in his thirties, with a convincing history of infection and early manifestations, and perhaps of some recurrent lesion, to be left to the mercy of his defence mechanism simply because at the time of examination he happens to have no gross signs except a positive blood Wassermann reaction. Such patients invariably deserve treatment. If the Wassermann reaction be negative, I advise either frequent observation, if the patient is easily accessible, or treatment “for life insurance.” Many problems of this latter kind constantly present themselves to the consultant in the persons of young men treated by the emergency standards of military service, by the rough-and-ready, inadequate technics of the inexperienced, or by such measures as the patient himself in his haste, ignorance, or poverty would undertake. The patient may be cured, but how be sure? I have been more and more inclined to fall back on frequent observation if the treatment has approached modern standards, the initial examination is completely negative at all points, the time since the last treatment two years or longer, and the prospects for co-operation good. The time is not far distant when the checking of these patients will include

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rabbit inoculations from their inguinal lymph nodes, and possibly also inoculations from semen. Such patients should not contemplate marriage if they can be dissuaded until three full years of complete freedom from symptoms, and until a total period of at least five years since infection has elapsed.

If more than five years has elapsed between an undoubted infection with grossly inadequate treatment and the first thorough re-examination, only individual judgment can decide whether the patient should be regarded as a serologically negative syphilis or a case of arrest or "cure." The spontaneously negative tendency of the blood Wassermann reaction puts untreated five-year and later cases into a different group from two-year and earlier cases. In the former the test may be spontaneously negative, the infection present, but progressive and degenerative in character. In the earlier cases it is much more likely that a positive test will be obtained if any spirochætal rests remain. Even though infections of less than two years' duration may be temporarily negative at one examination, the blood Wassermann reaction is likely to become positive if a recurrence develops. The foregoing general principles are, of course, influenced by such important considerations as the desire to lead an active sexual life, to marry, or to have children.

Active Process versus Residuum.—The decision as to whether one is dealing with an active syphilitic process or a residuum is sometimes extremely difficult. There is no object in treating a patient for a scar, such as a fixed pupil or an absent knee-jerk, which cannot, as a rule, be affected in any way. On the other hand, the mixture of scar and active inflammatory process which a case often represents can be materially benefited, the relief being proportional to the amount of active inflammation. For example, corneal vascularisation in interstitial keratitis offers little outlook for improvement. But if any evidence of activity in the form of punctate infiltrates can be found the response to treatment may be surprising. In such a case the decision to treat the patient for syphilis may rest entirely with a specialist in another field and be the result of an examination not available to the ordinary physician. In some cases, such as retrobulbar neuritis, recent eighth nerve deafness, Bárány syndromes in syphilitic patients, persistent subjective symptoms in

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neurosyphilis such as lightning pains and headache, and constitutional subnormality without localising signs, it may be desirable to treat because of the possibility of benefit. This is not a therapeutic test to establish the existence of syphilis, for the diagnosis may be perfectly apparent, but a test of the treatability of the infection. In all such cases treatment, once begun, must be pushed to completion in accordance with a reasonable modern standard. An average plan would call for three six-injection courses in a year and a half, with a course of forty inunctions between each two arsphenamin courses, a total of 200 rubs if well tolerated, and a month's rest interval before and after each mercurial course. Simply to relieve the symptoms and stop treatment disturbs the patient's defence mechanism, may definitely lead to some more serious form of relapse, and violates the first principle, "*primum non nocere*."

Active Benign Syphilis.—The management of benign but active syphilis is a step beyond the problem of latency, for the obligation to treat the patient is more apparent. At the same time it is important to keep fundamentals in mind, and to avoid exchanging a benign lesion and an effectively working defence mechanism for some serious loss of resistance and a flare-up of dangerous proportions. The patient who presents only trivial lesions of the bone and skin four or five decades after infection should not be pounded with the heavy artillery of modern treatment. In such cases it is even distinctly risky to use arsphenamin or neo-arsphenamin because of their allergy-producing properties. Resort may well be had in such cases to mercury and iodide by mouth, or slightly more intensive mercurialisation if necessary. On the other hand, in earlier life the appearance of even benign lesions must be the signal for thoroughgoing treatment and prolonged observation.

The Fixed Positive Blood Wassermann Reaction.—The management of the patient with a controlled or latent infection in whom treatment discloses a resistant blood Wassermann test is one of the trying problems of syphilotherapy. Wassermann-fast patients should not, in my opinion, be discharged from periodic careful re-examination, with special reference to the cardiovascular and nervous systems throughout life. The frequency of such examinations should be dictated by the gravity and

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extent of the original process and the degree of apparent resistance to treatment.

The question of the amount of treatment which it is proper to administer to a Wassermann-resistant patient is no more susceptible of exact definition and reply than are the many other questions arising from the problem of standard procedures in syphilotherapy. I have adopted as guides to treatment tentative principles as follows :—

(1) Search every accessible organ and tissue in the Wassermann-fast case by every clinically available method for evidence of syphilitic changes.

(2) Weigh the degree of activity of the process and the extent of damage and probable recuperative power of the most vital structure involved by the infection.

(3) Identify the weakest element in the patient's make-up and estimate the tolerance for arsenic and mercury of the structures which must bear the brunt of treatment by-effects, such as the liver, kidney, and skin.

(4) Do all that can be done to increase tolerance of treatment by protective measures, by extirpation of focal infection, and by selection of the therapeutic agents.

(5) Direct the treatment of Wassermann-resistant patients less toward overcoming the resistance offered by the Wassermann reaction, and more toward a satisfactory symptomatic response of the vital structures involved by the disease within the limitations imposed by the weakest element in the tolerance. Get all the symptomatic effect possible short of recognisable damage. If tolerance permits, give at least as much treatment as to a fully-developed secondary case. As a tentative maximum schedule corresponding to the treatment requirements for an early case, I should suggest four courses of weekly injections of arsphenamine, eight to the course, with three courses of bismuth, or mercury, intramuscularly and 100 to 150 inunctions, iodide being given by mouth before meals in 20-grain doses well diluted. If treatment is undertaken, and especially once the arsphenamines are begun, it defies the known facts about the immunology of the disease and its defence mechanism to give a few injections of neoarsphenamine (say four to six), with a few pills, and then to leave the patient, his equilibrium disturbed and his organisms, the exciters of his immunity reactions, in part destroyed, to become a prey to the first

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relapse that follows the revival of some local focus with vascular dissemination. It is better to confine the treatment of latency to mercury, iodide and bismuth than to institute an inadequate arsphenamine therapy or to fail to carry it through, if possible, to complete and persistent Wassermann negativity.

Vary the Mode of Attack.—Within the last two years bismuth and silver arsphenamin have both been mentioned in the literature as particularly effective in the treatment of Wassermann-fast patients who had received thorough general treatment without securing a negative blood Wassermann reaction. In 64 per cent. of McCafferty's twenty-five cases, for example, the strength of the positive Wassermann was diminished or all reactions rendered negative by one course of bismuth therapy. At the end of three courses only 23 per cent. of the cases remained Wassermann-positive. Behn and I reported favourably on the effect of sulpharsphenamin intramuscularly. All these methods of approach follow the fundamental principle in the treatment of resistant syphilis that varying the mode of attack is the best way to overcome a persistent infection.

The question of lifelong intermittent treatment for the patient with a persistent positive blood Wassermann reaction, as a routine practice without reference to evidence of progression or activity disclosed by examination and repeated observation, is one on which marked differences of opinion may justly exist. I know of no way in which to evaluate them at present. I can merely say for myself that, if initial treatment has been thorough, its indefinite prolongation must be purely a matter for decision in the individual case, conditioned by the type of involvement disclosed before the process came to apparent quiescence. In many cases I think it needlessly hard on the patient's physique and morale, and productive of serious risk of relapse, to stir up his defence mechanism from time to time and run the risk of nullifying its work by the short course of three or four arsphenamin injections on the one hand, or the inefficient use of mercurials on the other. Such half-way measures seem to be too often the practice of the lifelong treatment advocates.

Aphoristic summaries have an unfortunate trick of failing to say the one most important thing for the

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particular case with which the particular physician who reads them is called upon to deal. Yet I am tempted to gather the essence of this presentation into four phrases : Practice the complete examination of latency ; appraise the case individually ; think of the age of the infection and the life expectancy of the patient ; once begun, treat thoroughly ; release from observation—never.