VII

CRITICAL REVIEW: SYPHILIS

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Prophylaxis.—Increasing numbers of patients who have exposed themselves to possible infection twenty-four hours previously are demanding to be protected against syphilis. Excellent though the prophylaxis may be that is conferred by the classical mercurial inunction method of Metchnikoff, the superiority of the organic arsenical compounds to mercury is so great that the modern protection of the patient necessitates their use. Magian's experiment¹ at prophylaxis by the intravenous injection of arsenobenzol within twenty-four hours of inoculation was quite uncontrolled, is open to many other objections, and contains several sources of fallacy. To mention only one: the cerebro-spinal fluid was not examined. The necessity for this in such experiments, as well as in all cases of syphilis, is exemplified in an instance reported by Nadel² in which the diagnosis of primary chancre was made by the dark-ground method. Intensive arsenobenzol and bismuth treatment was instituted—about 4 grammes of "914" being given. Five months after the date of infection persistent headaches commenced, and the cerebro-spinal fluid showed a positive W.R. The blood remained persistently negative. Fournier and Guénot³ treated forty women who had had connection with men in whom infective lesions were present. These women had no clinical or other signs of previous lues. Six intravenous injections of arsenobenzol were given, and in no case did syphilis result. Michel and Goodman⁴ employed this method by giving three doses of 0.3 gramme of arsphenamin at intervals of from two to five days to thirty men, most of whom had had connection with syphilitic women. In no instance did infection supervene. The more recent experiments by Levaditi and Navarro-Martin with the acetyl derivative of oxyaminophenyl arsinic acid given orally, are of such interest and import-

CRITICAL REVIEW : SYPHILIS

ance that a forthcoming review will be devoted entirely to them.⁵

Apart from this latest series of investigations, none of the earlier experiments carry conviction. There were no controls, and, from the really practical point of view, they are valueless. Had each of the patients of Fournier and Guénot been actually suffering from primary syphilis, it is probable that after six intravenous injections of arsenobenzol they would show no clinical signs of the disease. Even at the present day six such injections are, unfortunately, sometimes considered sufficient to *cure* syphilis, let alone prevent it.

A recent study upon this question is that of Greenbaum and Harkins.⁶ Rabbits were used in this investigation, which was undertaken to determine the effect of arsenobenzol in doses equivalent to the adult human dose, as a prophylactic against syphilis. "Arsphenamin," "neo-arsphenamin," and "sulph-arsphenamin" were used. These are the terms applied in the United States for arsenobenzol, "914," and the French "sulfarsenol" respectively. It was found that the equivalent adult human dose of arsphenamin—0.6 gramme—did not prevent the development of syphilis even when given as early as three hours after inoculation; but that three such doses, the first given twenty-four hours after inoculation, and the remaining two at twenty-four-hourly intervals, did prevent it. With the other two compounds, exactly the same result was obtained in doses equivalent to the adult human dose of 0.9 gramme. Much of the positive knowledge regarding syphilis is derived from animal experiments, and, while in this instance—as in all others—certain modifications may require to be made in applying the findings to the human disease, the important point would appear to be that so far as human prophylaxis is concerned, the minimum for safety is three intravenous injections of the chosen compound in the indicated doses at twenty-four-hourly intervals, the first being given not later than twenty-four hours after exposure to infection. Although Politzer,⁷ as long ago as 1916, treated cases of early syphilis with three full doses of arsenobenzol at such intervals, an intensive bombardment of this kind with so powerful a drug is a proceeding accompanied by considerable risk.

Treponema pallidum.—It is not always possible to have

BRITISH JOURNAL OF VENEREAL DISEASES

recourse to the dark-ground method for the demonstration of this organism. Dubosarsky⁸ recommends staining with "spirsil," which is an ester of triphenyl methane. Films are made in the usual way, fixed in alcohol, washed in water, and then stained for from two to three minutes. The organisms appear deep red in colour and are easily recognised. Brown and Pearce⁹ have shown that in the rabbit *Treponema pallidum* can penetrate undamaged mucous membrane such as that of the conjunctival sac or prepuce. Infections which occur in this manner were found to pursue a very mild course. Although this may furnish some explanation of *syphilis d'emblée*, usually in cases of cryptogenetic syphilis, the disease is very severe in type.¹⁰ Studying the motility of the organism, Oelze¹¹ found its activity to be greater in solid tissues than in blood. This observation may be of some importance in throwing light upon the problem as to the genus to which the organism belongs. Weiss and Wilkes-Weiss¹² have investigated improved methods for the isolation and cultivation of *Treponema pallidum* in pure culture. Various media were experimented with, and the conclusion was that, for optimum growth, the initial reaction of the medium should be pH 7.5 to 7.9. If the acidity is in excess of 6.9, growth does not take place.

The nomenclature of the causative organism of syphilis has given rise to a great deal of discussion, and that general agreement has not yet been reached is evident from the fact that in the previous issue of this Journal it received three different designations. The whole point of the controversy appears to lie in whether the organism belongs to the protozoa or to the bacteria. Almost every investigator has propounded a new classification, and coined a new nomenclature. There are three schools of opinion: one regarding it as a bacterium; another as a protozoön; while a third places it in an intermediate class—the "protista" or "protoflagellata." One's personal view is that it is a protozoön. It has been pointed out¹³ that there exists an affinity that is almost specific between the elements composing the fifth group of Mendelieff's periodic series and protozoal organisms,—and especially that of syphilis. The course of the disease, its pathology, its hereditary nature, the behaviour of the organism in culture, all incline one to this opinion. In these reviews,

CRITICAL REVIEW: SYPHILIS

therefore, the organism will receive the designation "*Treponema pallidum*," given to it by its discoverer. It is of interest to note here, that in 1907, MacLennan^{14,15} expressed the view that the organism in its spiral form was only one part of its life cycle, and he demonstrated what he took to be some of its variations. Such a life cycle has not been established, but if in the future it should be, any merit that there may be in priority belongs to MacLennan.

Serological.—The need for a standardised serological test for the diagnosis of syphilis is clamant. There cannot but be confusion so long as the positive of one laboratory is the negative of another further along the street. The symbols used to indicate the strength of the reaction should be the same from China to Peru. At present, interpretations such as "four plus," "C₁," "weakly positive," and such like are vague and unscientific. They convey different meanings to different readers. The witness who described a stone with which an assault was committed as being "the size of a lump of chalk" conveyed an idea to the judge, but little more definite than does the bare term "weakly positive" with regard to a W.R. The Ministry of Health has recently accepted the League of Nations Health Committee's proposals for a standard notation. Strongly positive reactions are to be reported as "++"; positive reactions which are diagnostic are to be designated "+"; doubtful reactions which are not diagnostic are to be returned as "±"; and negative reactions as "— —."¹⁶

In five years' observation of the Wassermann test, as carried out in the Manchester Public Health Laboratory, one is of the opinion that the method there adopted is of particular value, not only in gauging the effect of treatment and in controlling it, but in making a prognosis as to the amount of treatment which will be required. In the Manchester technique the M.H.D. of complement is the strength of the dilution at which *complete* hæmolysis occurs. The complementary value of the guinea-pig serum is estimated in the presence of human-heart-muscle-and-cholesterin antigen. The complement for the test is used at a strength of three M.H.D.'s. The reading of the test is done after the tubes have been in the ice-chest overnight, the amount of hæmolysis being measured with the aid of a comparator. "Standard fixation" means com-

BRITISH JOURNAL OF VENEREAL DISEASES

plete inhibition of hæmolysis. The system of reporting is as follows :—

<i>Notation.</i>	<i>Standard Fixation.</i>
(1) NEGATIVE	—
(2) DOUBTFUL	1 in 1 to 1 in 2 dilution.
(3) Weakly POSITIVE	1 in 3 to 1 in 8 „
(4) POSITIVE	1 in 10 to 1 in 20 „
(5) Strongly POSITIVE	1 in 25 to 1 in 45 „

For practical clinical purposes one does not, in the absence of clinical signs, diagnose syphilis unless the report is at least No. 3. If, however, the patient is one who has been treated, or whose W.R. has at any time been positive in the notations numbered 3, 4, or 5, then a “doubtful” report, as No. 2, is taken as an indication for further treatment until a definite and permanent negative after provocation is obtained. Although Harrison¹⁷ enumerates some fifteen non-syphilitic conditions in which positive results have been reported as occurring, a survey of the literature for the last decade indicates that as technique has improved, the number of reports of non-specific reactions has decreased. One is inclined to regard such reports as either evidence of faulty technique, or that the person from whom the serum was obtained was suffering from endosyphilis¹⁸. Rovidá¹⁹ states that scarlet-fever patients may give a positive Wassermann and Sachs-Georgi reaction; but this applies to uninactivated serum. Both reactions are negative if the serum is inactivated at 56° C. With negative reports as to the blood alone, where provocative injections have not been given, one may have a good deal of uncertainty. The grave disadvantages of having had the same blood reported as negative from four laboratories, and as positive in a dilution of 1 in 5 from another, are obvious.

Ruder²⁰ states that the latest modification of the Meinicke test is valuable on account of its sensitivity and technical simplicity. There is, however, a tendency to unspecific results, so that it should only be used in conjunction with the Wassermann and Sachs-Georgi. Poehlmann²¹ found that the third modification of this test, which has been definitely abandoned by Meinicke, is often, in obvious cases of syphilis, negative. Investigating the Kahn test in G.P.I., Dudgeon²² considers it good confirmation of the W.R., and that it is specially suitable as a routine one in institution work. Gaston and Bethoux²³

CRITICAL REVIEW: SYPHILIS

show that the Hecht modification of the W.R. is more sensitive and more valuable than the Vernes reaction.

Belding and Holmes²⁴ find that the strength of the W.R. in congenital syphilis is greater than in the acquired disease of the same duration. The congenital case bears the greater syphilitic burden; it is fully laden perhaps from the moment of conception; if the last straw has been added, the pregnancy does not go to full term. The patient with acquired syphilis is a pot in which is planted a luetic seedling; the congenital case is itself a fully-developed syphilitic plant which has been introduced into the community's conservatory. After birth the strength of the W.R. gradually decreases and may recede to such a degree as to become evident only after provocation. This is often erroneously attributed to treatment. The practical danger is that the unwary may be tempted to cease treatment, or to refrain from commencing it. Although such a child is syphilitic, it may present no signs, until the occurrence of, say, interstitial keratitis at puberty. The influence of these great changes, birth, puberty, pregnancy, the menopause, and death, upon the W.R. is very obscure. Careful research upon these matters would be extremely valuable. One would suggest the possibility that these constitutional storms, acute fevers, and such like, have the effect of stimulating an endosyphilis into exhibiting itself by giving a positive W.R.

The object of Cruickshank's recent study²⁵ was a very desirable one, although it will not be generally accepted that his conclusions are warranted by the evidence produced. One's view is that no matter what may be the serological condition after birth, the treatment of a child born with a positive W.R. should extend till adolescence.²⁶ The luetic child is born with *adult* syphilis. The adult acquires *infantile* syphilis, which may take years to reach maturity. It is not considered that the criteria adopted by Cruickshank for the diagnosis of ante-mortem and post-mortem syphilis were adequate. With regard to the former there is no mention of provocation, or of lumbar puncture having been done. For the post-mortem diagnosis he seems to have relied almost entirely upon the pre-treponeme conception of the pathology of the disease, in which hæmorrhage, fibrosis, and the gumma figured so largely. The Levaditi method for the demonstration

BRITISH JOURNAL OF VENEREAL DISEASES

of the organism is mentioned, but there is no indication that the special organs of predilection were specially searched. Details of the histological examinations are not given—neither as to the organs selected nor as to the appearances considered characteristic of syphilis. There is no mention of the method of the animal inoculation of suspect material, nor of the dark-ground examination of emulsified organ tissue. Attempts to find the treponema are not likely to be very successful unless they are prosecuted in its favourite haunts. Cruickshank does not seem to have made any very definite effort to discover the presence of the very distinct and typical histological lesions pointed out by Warthin.²⁷ These mild inflammatory reactions, characterised by lymphocyte and plasma-cell infiltrations, especially in the stroma surrounding blood-vessels and lymphatics, are the precursors of definite fibrosis and gummata, and are caused by relatively avirulent organisms. They are most frequently found in the nervous and vascular systems, the wall of the right ventricle, the pancreas, suprarenals, and genital glands. The post-mortem diagnosis of syphilis is essentially *histological*, and unless it is so based its value is but little. No doubt when the teaching medical schools, with their wealth of clinical and post-mortem material, have keen and modern venereological departments attached to them, histological examinations of autopsy material for syphilis will be carried out along these lines, with valuable results.

Belding and Holmes draw attention to the fact that untreated or but slightly treated children respond much more readily to remedial measures than do those who have received a fair amount of treatment. The same holds good in acquired syphilis which has not been thoroughly or scientifically dealt with. A "treatment fast" condition is induced in which *Treponema pallidum* has developed an immunity to the drugs used, and in which persistence along the same lines will only result in riveting the condition more firmly upon the patient.

Glynn, Roberts, and Bigland²⁸ have studied the Wassermann-relapse incidence in 503 patients who had what is described as the "standard" course of six intravenous injections of arsenobenzol and eight intramuscular mercurial ones. Over 60 per cent. of these patients received continuation courses of mercury either in the

CRITICAL REVIEW : SYPHILIS

form of grey oil or tablets. Of these there were 185 W.R. relapses. The relapsed cases were again treated in a similar manner, and thirty-five relapsed a second time. In other words, there were 36 per cent. of first-relapses, and 19 per cent. of second-relapses. Those who had received continuation treatment relapsed more frequently than those who had not. Apart from these results—and they merely emphasise it—the initial treatment was utterly inadequate. One is constrained so to express it because the authors of the paper do not attempt to stress the fact. It is surprising to find such a small quantity of intravenous arsenobenzol being adopted as a standard. Even by the intramuscular route such an amount could hardly be considered sufficient. This communication illustrates well the futility of considering a negative *unprovoked blood W.R.* to be synonymous with cure. The use of mercury as first understudy to arsenic is, since the advent of bismuth, obsolete. Its potency as a treponemicide is comparatively trivial; as a tissue-poison its effect is greater than its antisyphilitic power, but that it has a certain mild provocative use is well shown by the above results. A study of that most valuable book to the modern syphilologist, Hutchinson's "Archives of Surgery," will show that most of the cases of malignant syphilis and phagedæna which passed through his hands had been subjected to what would now be considered a savage mercurialisation. The W.R. done in the 503 cases referred to, and showing a negative result after "standard" treatment, might possibly under another technique have given a positive result with standard fixation in a dilution of 1 in 3. As the effect of the arsenic wore off, or as the provocation from the mercury manifested itself, this positiveness might increase until standard fixation occurred in a dilution of 1 in 8 or 10, and only then might it declare itself as a definite positive under the technique used by the authors of the paper. This investigation shows the great need there is for an adequate minimum standard routine treatment, especially for early syphilis. One's own experience is that the minimum that is consistent with safety is eight weekly injections of "606" in as full doses as can be tolerated intravenously, succeeded by twelve tri-weekly intramuscular injections of metallic bismuth; and then both repeated without an interval, before investigating the

BRITISH JOURNAL OF VENEREAL DISEASES

reactions of the blood *and cerebro-spinal fluid*. The administration of iodine in large doses, *e.g.*, potassium iodide, gr. xxx t.d.s., for four weeks should precede further Wassermann tests. These should be done quarterly, commencing three months after the last bismuth injection. In a series of 172 primary syphilitics so treated, there have been no blood or cerebro-spinal fluid W.R. relapses twelve months after the cessation of treatment in spite of provocation. Some of these are now being tested after provocative sterile-milk injections. This was suggested by the findings of Radnal²⁹ that in some cases of treated syphilis which were sero-negative, provocative injections of arsenobenzol had no effect, but that the use of a non-specific milk preparation or of bismuth intramuscularly was followed by a positive blood W.R.

Therapy.—The difference of opinion regarding the therapeutic value and action of mercury expressed by Lomholt and the writer, in the previous issue of this Journal, makes it necessary for the latter to indicate the evidence upon which his opinion is based. The basis of comparison between bismuth and mercury would be their relative power of cure in a case of experimental syphilis, in their maximum tolerated doses, expressed in terms of metallic bismuth and metallic mercury. Nichols³⁰ found that mercury had no action upon *Treponema pallidum* in amounts much short of the lethal dose. The tolerated dose of mercury salicylate is 0.005 gramme per kilo of body weight, or, expressed in terms of pure mercury, 0.0029 gramme. The tolerated dose of the salicylate has no curative effect. A dose of 0.0075 gramme per kilo will quickly destroy treponemata, but is fatal to the animal. Although the tolerated doses of the mercurial salts differ widely, yet, when calculated in terms of metallic mercury, they are practically identical. The tolerated dose of mercury may, therefore, be taken as 0.0029 gramme per kilo. The margin between the parasitotropic and organotropic effects of mercury is extremely narrow even for the parasites which are most susceptible to it. There is, in fact, no such thing as a single curative dose of mercury for animal syphilis; so that it does not possess a C/T co-efficient. Levaditi has shown³¹ that the *curative* dose of bismuth is 0.000317 gramme per kilo. This is *more than nine times less than the tolerated dose of mercury which does not cure*. This experimental evidence as to the

CRITICAL REVIEW: SYPHILIS

relative powers of cure is amply borne out by clinical experience. That the toxic effects of these two drugs are equally different is, one thinks, equally clear.

The question as to whether mercury acts directly or indirectly upon treponemata has occasioned some discussion. Lomholt and Kissmeyer³² are reported—the original is not available—to have found that the highest concentration of mercury in the blood at the height of a course of mercurial treatment was no more than 1 to 3 mg. per litre. They tested the effect of concentrations of mercury bichloride of 5, 10, 20, 30 and 40 mg. per litre upon the treponemata in culture. In five days there was rich growth in the 5, 10, and 20 mg. per litre tubes. From this they concluded that mercury acts *indirectly* upon the organism of syphilis.

Lee³³ found that mercury bichloride (1 in 1,000) inhibited the motility of treponemata in twenty minutes, and destroyed them in twelve hours. Benzoate of mercury (1 in 450) likewise inhibited motility in twenty minutes, and caused complete disappearance of the organisms in twenty-four hours. He also showed at the same time that salvarsan (1 in 130), neo-salvarsan (1 in 130), silver salvarsan (1 in 125), salvarsanised serum, and neo-salvarsanised serum did *not* kill these organisms in twelve hours. *Salvarsanised tissue extract*, however, *did* destroy them in from six to twelve hours. He concluded from these observations that mercury acts *directly*, while salvarsan acts *indirectly* by forming a lethal arseno-protein—just as Levaditi showed that bismuth does by forming a bismo-protein or bismoxyl.

Although it be true that Lee's concentrations of mercury were very much higher than that found by Lomholt and Kissmeyer to occur in the blood, it is not clear why this should be considered as invalidating his experiments as to direct or indirect action. The concentrations of his arsenical solutions were equally high. His argument is: "Mercury kills treponemata in twelve hours; arsenic does not kill them in twelve hours—both being allowed to act directly. Arsenic plus tissue extract kills them in from six to twelve hours, therefore arsenic acts indirectly by combining with something in the tissues to form a lethal arseno-protein." He is undoubtedly right so far. Is he justified in deducing from his evidence that mercury acts directly? The reviewer is inclined to

BRITISH JOURNAL OF VENEREAL DISEASES

think that he is, at the very least, justified in attributing the greater part of the slight antiluetic power of mercury to its *direct* action. One does not admit the experiment of Lomholt and Kissmeyer as proof of indirect action. If it can be demonstrated that solutions of mercurial compounds in fairly high concentrations—like those of arsenic, bismuth, and antimony—exert no treponemicidal effect in a certain time, but that when they are combined with tissue extracts they do produce a lethal effect in the same or a shorter time, then only can the case for indirect action be proved. That proof is available for the other anti-syphilitic drugs, and mercury must fulfil the same criteria.

It is of vital importance that the relative potency and merits of the various antisyphilitic drugs should be thoroughly appreciated, as upon this depends the health of, perhaps, 10 per cent. of the population of these islands. Bismuth is essential in the modern treatment of syphilis, and as it is within the scope of the general practitioner who may be remote from treatment centres and syphilologists, it is necessary in his patients' interests that he should realise its vast superiority to mercury in any form.

Kolle ³⁴ found that mercurial preparations were practically inert in aborting experimental syphilis; but that when rabbits were given intramuscular injections of bismuth, testicular inoculations with *Treponema pallidum* gave negative results even when the interval between the injection and the inoculation was as long as fifteen weeks.

Information is now becoming available as to recurrences after bismuth treatment. Simon and Bralez ³⁵ record seven cases from a consideration of which they are of the opinion that at least 2 grammes of bismuth are necessary to prevent neuro-recurrence. The intervals between the cessation of treatment and the recurrence varied from two to twelve months. In one patient who seemed to be refractory to bismuth, the recurrence appeared in less than one month after three series of injections, totalling 9.5 grammes. This is but added evidence that treatment should not be by one drug alone, but that arsenic and bismuth should be given in alternate series. Hudelo and Rabut ³⁶ draw attention to the fact that recurrences of secondary syphilis may take place not only after an

CRITICAL REVIEW : SYPHILIS

intensive and prolonged treatment, but even during it. In such cases the W.R. may be negative. Such instances are not common, and their cause is obscure. A virulent strain of treponema, a want of reaction on the part of the patient in forming arsenoxyl or bismoxyl, insufficient dosage, allergy, have all been invoked as explanations. Kryle³⁷ found that combined protein and antisypilitic medication was satisfactory in changing a persistently positive W.R. into a negative one. Greenbaum and Wright³⁸ treated thirty-five syphilitics by this method. A preliminary course of six intramuscular injections of a 4 per cent. sterile milk protein was given at intervals of two to three days. This was followed by a series of weekly "914" injections. In two secondary and in two tertiary cases the lesions had practically disappeared under the protein therapy alone. One patient, with paralysis of the sixth nerve and diplopia, had completely recovered after the sixth protein injection. In one secondary case there was, after each protein injection, a definite Herxheimer reaction. A persistently positive blood W.R. was present in twenty-nine of the patients; three became negative after the protein series and four "914" injections. In the remainder there was no change.

Untoward Effects.—Courcoux and Boutelier³⁹ describe an intensely pruritic urticarial eruption occurring after bismuth injections. The flexures were especially affected, the face, hands, legs, and feet escaping. Two months afterwards erythematous-squamous plaques, pigmented follicular papules, and various pigmented patches remained. Magnus⁴⁰ describes a patient who had been treated for early syphilis with eight injections of 0.6 gramme of "914," and then with six *intravenous* injections of a bismuth preparation. After the sixth bismuth injection he suddenly collapsed and died. Such an occurrence is solely due to a complete misapprehension as to the mode of action of bismuth as a treponemicide in the body. The intravenous administration of bismuth is essentially wrong. Given in that fashion its anti-syphilitic power is practically *nil*, but its toxic effect is ten times greater than when injected into the muscles.

The nitritoid crisis sometimes occurring after the administration of arsenobenzol has been investigated by

BRITISH JOURNAL OF VENEREAL DISEASES

Rosen, Muller and Myers⁴¹ in its relationship to silver-arsphenamin and to the involuntary nervous system. They conclude that every injection of arsphenamin is followed by a decrease in the leucocytes in the peripheral vessels. In the nitritoid crisis this decrease is very marked. The injection of silver-arsphenamin is usually unaccompanied by a peripheral leucocyte decrease, showing that there is no reaction of the involuntary nervous system. Exceptions to this rule are found only in the few persons who develop a nitritoid crisis after arsphenamin. They consider that this proves that any reaction after silver-arsphenamin is not due to the drug, but to previous disturbance of the involuntary nervous system. Pomaret⁴² believes that the nitritoid crisis is due to the phenol radical in the arsenic preparation, and that it can be explained by the simple physical alterations that take place in the blood upon the introduction of a compound of phenol.

McBride and Denny⁴³ recommend sodium thiosulphate given intravenously in poisoning due to arsenic, bismuth or mercury. It should be put up as a dry sterile powder in doses of 0.45, 0.6, 0.75 and 0.9 gramme. The dose should be dissolved in 5 c.c. of distilled water and given intravenously. No toxic symptoms occur even if as much as 2 grammes are given. This substance is so valuable an antidote that it should always be kept handy for emergencies. In a case of fatal poisoning by any of the anti-syphilitic remedies censure might be given if this substance had not been used. Semon⁴⁴ is impressed with its value in arsenical dermatitis, bismuth stomatitis, and arsenical jaundice. Wilhelm⁴⁵ emphasises the value of duodenal lavage in jaundice complicating the treatment of syphilis. Thirty-three cases were dealt with, and 90 per cent. recovered definitely and rapidly under this method. As a rule, two lavages were necessary. The method was found to be excellent in controlling the nausea and vomiting. His experience tends to show that arsenic is not necessarily the causal agent in this type of jaundice, and this is in agreement with Zimmern,⁴⁶ Scott and Pearson,⁴⁷ and Hallam,⁴⁸ who suggested that it may occur in an epidemic form. The value of the Van den Berg test in detecting latent jaundice during arsenobenzol treatment is emphasised in a valuable paper by Gerrard.⁴⁹

CRITICAL REVIEW: SYPHILIS

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