

THE LUETIN REACTION IN SYPHILIS.

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Noguchi's luetin consists of killed cultures of the *Treponema pallidum* emulsified with the media in which they have been cultivated. The use of this preparation in the diagnosis of syphilis is analogous to that of tuberculin in von Pirquet's test for tuberculosis; that is to say, if it be injected into the skin during certain stages of syphilitic infections it produces a cuti-reaction.

Noguchi's first experiments were made with rabbits artificially infected with syphilis and, led by the encouraging results which he obtained with these animals, he employed his preparation in the detection of the disease in man. He found that, in the majority of normal persons, 24 hours after the injection a small erythematous area appeared at the point of inoculation, which subsided in 48 hours. On the other hand, in the skin of syphilitic persons the injection of luetin frequently produced certain well-defined lesions of which he distinguished the following three forms.

1. *The papular form.*—An indurated papule, 5 to 10 millimetres in diameter, appears in 24 to 48 hours. The papule increases until the fourth or fifth day, after which it subsides gradually and disappears by the end of the second week.

2. *The pustular form.*—The reaction pursues the same course as the papular form until the fifth day, when, instead of becoming smaller, it increases in size, the central portion softens, and a vesicle forms which rapidly becomes pustular. This ruptures, and a scab forms which falls off in a few days. There is a wide range in the intensity of this reaction. Noguchi found that this form occurred almost constantly in tertiary syphilis and also in cases of secondary and hereditary syphilis which had been treated with salvarsan.

3. *The torpid form.*—In rare instances, though no positive result follows the injection during the first ten days, at the end of that time, or after an even longer interval, a pustular reaction occurs.

Noguchi found that in syphilitics the reaction varies according to the stage of the disease and the treatment which the patient has received. In untreated primary and secondary cases the result is generally negative; occasionally there is a papular reaction. In secondary cases treated with salvarsan the result is positive in more than 70 per cent. In tertiary and hereditary cases the reaction is intense and almost constantly positive.

The sample of luetin which was employed in the investigation under consideration was received from Dr. Noguchi on June 13th, 1914. The first injections were made four days later, and the series of inoculations were completed on August 12th.

As a control to the luetin an emulsion was made which consisted of the same constituents as that preparation except that it contained no *treponemata*. It was prepared according to Noguchi's original method. Two per cent. agar-medium was ground up in a mortar and ascitic fluid added until a mixture was obtained which passed readily through a fine hypodermic needle. Carbolic acid was added to the amount of 0.5 per cent. The fluid was put up in glass capsules, each containing 0.5 c.c., and these were heated for one hour at 60° C.

In accordance with Noguchi's instructions, the test was applied in the following manner. The skin of both forearms was rubbed with pledgets of cotton-wool soaked in a solution of lysol. The injections were made, not subcutaneously, but into the superficial layers of the skin, by means of a tuberculin syringe armed with a very fine needle. A successful inoculation raises the epidermis in the form of a flattened papule, whiter than the surrounding skin, very much like a "nettle-sting," and of about the same duration. In each instance about 0.07 c.c. of equal parts of luetin and salt solution were injected into the left forearm and a corresponding amount of the control emulsion into the right.

The patients among whom this investigation was carried out were all Asiatics (chiefly Chinese) of the coolie class. They were inmates of the Federated Malay States Government hospitals, and I am indebted to the medical officers in

charge of these institutions for permitting me to undertake this work in their wards. Two groups of patients were examined: (1) a group of persons who were either under treatment for syphilis or were believed to have suffered from that disease; and (2), as a control to the first, a number of persons suffering from diseases other than syphilis.

TABLE I.—Results of Luetin Reaction in a Group of 130 Syphilitics.

Primary (9 cases. 33% positive.)		Negative 6	.....	Positive 3	{ Papular 3 Pustular 0
Secondary (42 cases. 57% positive.)	{ Active ...	Negative 15	.....	Positive 21	{ Papular 12 Pustular 9
	{ Latent ...	Negative 3	.....	Positive 3	{ Papular 2 Pustular 1
Tertiary (73 cases. 70% positive.)	{ Active ...	Negative 13	.....	Positive 34	{ Papular 20 Pustular 14
	{ Latent ...	Negative 9	.....	Positive 17	{ Papular 6 Pustular 9 Torpid 2
Doubtful (6 cases. 1 positive.)		Negative 5	.....	Positive 1	{ Papular 1 Pustular 0
		Negative 51	.....	Positive 79	

The results of the test as applied to the first group, which consisted of 130 individuals, are shown in Table I., where it can be seen that in 79 cases the reaction was positive and in 51 it was negative. The proportion of positive results was least in primary syphilis, greater in secondary, and greatest in the tertiary stage of the disease. In primary syphilis 3 out of 9 reacted positively; in the secondary stage, 24 out of 42; and in tertiary syphilis, 51 out of 73.

As is shown in Table I., the most common form of positive reaction was the papular type. This was the case in every stage of syphilis, except the latent tertiary form, in which there were only 6 papular reactions out of 17 positive results. Among these 17 were included two torpid reactions which occurred in a couple of old men from an infirmary. They both denied that they had ever suffered from syphilis, and both of them gave negative Wassermann reactions; one was blind from old ophthalmia, and the other had many scars which looked like the marks of old syphilitic sores. In the first case the reaction appeared on the fourteenth, and in the second on the eleventh, day after the luetin had been inoculated. One of these patients had been tested about a year before with a different sample of luetin, and on that occasion also he gave a torpid reaction.

In the negative cases the marks of both the luetin and the control punctures had disappeared in about 48 hours. In most of the positive cases a small red papule commenced to appear on the third day at the site of the luetin inoculation. This papule increased until the fifth or sixth day, when it was about the size of a pea. In the papular form the lesions subsided gradually and disappeared at the end of the second week. In the pustular form a red areola appeared round the papule and the centre became cyanosed and softened on about the sixth day. On the eleventh or twelfth day the resulting pustule usually ruptured and discharged a curdy, watery fluid, after which it quickly dried up under a scab and left a pigmented patch which gradually faded. In several instances the contents of these pustules were drawn off with an aspirating syringe and inoculated on to agar, but the latter always remained sterile.

In 4 of the secondary and 5 of the tertiary cases there was a reaction at the site of the control inoculation. In 7 instances this reaction was of the papular type, while

TABLE II.—Results of the Wassermann Reaction in 109 Patients belonging to the Syphilitic Group.

Stage of syphilis.	In agreement with luetin reaction.	Not in agreement with luetin reaction.	
Primary { Positive ...	2	4	= 6
{ Negative...	0	1	= 1
Secondary { Positive ...	19	10	= 29
{ Negative...	2	5	= 7
Tertiary { Positive ...	25	10	= 35
{ Negative...	8	23	= 31
Totals ... ..	56	53	= 109

at the point where the luetin had been injected there was a pustular reaction. The 2 remaining cases had pustules on both arms, but the pustules on the right (the control) side were smaller, and disappeared sooner than those at the site of the luetin inoculation. Noguchi

observed a similar phenomenon in 5 per cent. of his cases, and he ascribed it to that peculiar hypersensibility of the skin which sometimes occurs in syphilis and which Neisser has called "*Umstimmung*."

In Table II. the results of the Wassermann reaction are compared with those of the luetin test. Seventeen of the patients were not examined by the Wassermann reaction, because blood could not be obtained for the purpose, and in 4 other cases, where the reaction was negative, the diagnosis of syphilis was rather doubtful, so these were excluded. There remained 109 patients, belonging to the group of syphilitics, who were submitted to both the Wassermann and the luetin tests. The results were as follows:—

(1) Primary syphilis, 7 cases.			
Positive Wassermann reactions	...	...	6
Positive luetin reactions	...	...	3
(2) Secondary syphilis, 36 cases.			
Positive Wassermann reactions	...	...	29
Positive luetin reactions	...	...	24
(3) Tertiary syphilis, 66 cases.			
Positive Wassermann reactions	...	...	35
Positive luetin reactions	...	...	48

In the primary and secondary cases the Wassermann reaction was more frequently positive than the luetin test; but in the tertiary stage of the disease the reverse was the case and, as is shown in Table II., there were 23 cases of tertiary syphilis which gave negative Wassermann but positive luetin reactions.

There was no more agreement in the results of the two reactions than is accounted for by chance; in the series of 109 cases the results were the same in 56 and at variance in 53. This shows that the substance which gives rise to a positive Wassermann reaction is not the same as the substance which causes a positive response to an injection of luetin.

Of the 109 syphilitic cases 99 reacted positively to one or to both of the tests; in the remaining 10 both reactions were negative. As showing the danger of attaching too much weight to the results of these tests when the reactions are negative it may be profitable to consider these 10 cases in some detail. Two of them were in the secondary stage of the disease. One of them, who was suffering from iritis and polyarthritis, stated that he had had a primary sore a year ago. The other had been infected for three months; there was not the slightest doubt about the diagnosis, for he had a typical macular eruption and a healing chancre in which the *Treponema pallidum* was found. The luetin and Wassermann reactions in this case were both negative. The latter was found to be negative on three different occasions; once, 48 hours after an intravenous injection of neosalvarsan. Tested a fourth time, two weeks later, it had become faintly positive.

In the group of tertiary syphilitics there were 8 cases in which both the Wassermann and luetin reactions were negative. In 4 of these 8 only the scars of the disease remained, situated in two instances in the spinal cord with resulting paralysis, and in two upon the surface of the head and body; the process was no longer active and the primary sore dated back some 20 years or more. In all of the 4 remaining cases active lesions were present; 2 had ulcers, 1 a necrosed tibia, and the fourth was suffering from multiple gummata of the long bones. In the last case the diagnosis was beyond dispute. That is to say, in this series of 109 patients examined by the Wassermann and luetin reactions there was at least one case of active secondary syphilis and one case of active tertiary syphilis in which both reactions were negative.

As a control to the results of the luetin reaction in the group of 130 syphilitics, it was necessary to investigate its action on persons who were free from syphilis, and, for this purpose, the test was applied to a second group composed of 82 persons suffering from other diseases. This second group comprised 40 cases of beri-beri, 20 cases of malaria, and 22 of leprosy. Eight of the beri-beri patients, 4 of the malaria patients, and 7 of the lepers either had scars on the penis or gave a history of syphilis. The Wassermann reaction was positive in 4 of the cases of beri-beri, and in 2 of the patients who were suffering from malaria. Of the 22 lepers, 13 gave positive Wassermann reactions, but several of them had been selected for the luetin test on this account. All of the 82 patients in this control group reacted negatively to luetin with the exception of one man with beri-beri who had contracted syphilis ten years before.

It appears, then, that the action of luetin is specific: positive results occur only in syphilis; but in cases of this disease the proportion of positive reactions observed here was much smaller than that obtained by Noguchi.

It may well be that imperfect storage had impaired the reliability of the sample of luetin employed in this investigation. The efficiency of luetin, in the tropics at least, appears to be impaired by keeping. If the preparation could be kept continuously in a refrigerator, as Noguchi recommends, it is possible that this deterioration might be avoided. In a former investigation the specimen of luetin employed was nine months old and had been exposed to varying temperatures on its journey from New York to the Federated Malay States. Noguchi has stated that when luetin is examined under the dark-ground microscope it is seen to contain about 70 dead *T. pallida* in each field, but in this old specimen not more than a tenth of that number could be recognised, and when it was re-examined three months later the number of organisms had become still further reduced. In the present investigation the sample of luetin employed was about one month old when the series of inoculations was commenced, and three months old when it was finished. It contained about 35 *T. pallida* in a field (1/12 objective and No. 6 ocular). It was stored in a refrigerator, except when it was used in country districts; but on its journey through the post, from the Rockefeller Institute to Kuala Lumpur, it must have been exposed to varying temperatures and it appears to have deteriorated. Such sensitiveness to conditions of temperature detracts from the utility of luetin.

Difference of treatment may also have been a factor in producing discrepancy between the results of luetin inoculations here and those obtained by Noguchi in America. As a result of his investigations into the effect of antisymphilitic treatment upon the luetin reaction Noguchi has concluded that: (a) mercurial treatment may bring out the reaction in those cases in which it has not yet become positive, but such treatment has little or no effect upon the reaction when it has once developed; (b) salvarsan acts very powerfully in bringing out the reaction. Its subsequent continued use may eventually cause the reaction to become negative; probably by destroying the spirochaetes and curing the patient.

As the luetin reaction is influenced by treatment it is clear that uniform results will not be obtained in places where there is a great divergence in the lines of treatment adopted. One quarter of the cases investigated by Noguchi had received injections of salvarsan, and a large proportion of the remainder had undergone a thorough course of mercury. The treatment of syphilis on modern lines has not yet been adopted in the Government hospitals of the Federated Malay States; only 6 of the 130 syphilitics examined by means of the luetin reaction had received injections of neosalvarsan, and in only 2 of these cases had the injections been repeated. Six patients had been treated with mercurial inunctions, four with mercury powders and two with injections. The remainder of those who were under treatment had been given small doses of the perchloride of mercury (0.003 to 0.004 gm.) in the form of the liquor hydrargyri perchloridi of the British Pharmacopœia.

**Conclusions.**—The results of the luetin test in the group of syphilitics examined in the course of this investigation were not so frequently positive as in the cases examined by Noguchi and other observers in America. This divergence of results is probably due to: (1) the deterioration from storage of the sample of luetin employed here; (2) differences in the methods of treatment in force in the Federated Malay States and the United States respectively. No positive reactions were obtained in persons free from syphilis; they occurred in syphilitics only. The luetin test is so easily carried out that it would be of the greatest use in general practice if one could always decide, from the result of its application, whether a patient were, or were not, free from syphilis. Unfortunately this is not the case, for while a positive reaction is of great significance, a negative result does not exclude syphilis. When performed in conjunction with the Wassermann reaction the luetin test is of great value; in the early stages of syphilis the Wassermann reaction, and in the later stages the luetin reaction, is more constantly positive. In the great majority of instances one or other reaction is positive; but in a given case, even though both reactions be negative, syphilis is not absolutely excluded.

# THE SURGICAL USES OF OZONE.

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THE accompanying tabulated statement of the results of the first 21 cases treated by ozone at the Queen Alexandra Military Hospital cannot be regarded as anything but satisfactory from every standpoint, be it humanitarian, scientific, or economic. The cases were, for the most part, those of cavities and sinuses in the femur and tibia. It is the experience of those who have seen a great deal of war surgery that such cases obstinately resist treatment and are apt to remain unhealed for months and years.

The treatment consists of the application of ozone to the affected parts; it is, therefore, necessary to have an apparatus for generating ozone which shall be portable and easily worked. The one I am accustomed to use is known as Andriolis' ozoniser. It is called into operation by a four-volt battery animating a  $\frac{1}{4}$ -inch sparking Rhumkorff coil. The oxygen passes from a cylinder through the ozoniser, and in doing so comes in contact with a metal armature, the effect of this being to transform the oxygen into ozone.

Table of Wounds, Sinuses Treated by Oxygen and Ozone.

No.	—	Nature of disability.	Pre-vious duration.	Dura-tion of treat-ment.	Result.
1	J. B., Lincolns.	Compound comd. fracture of femur resulting in cavity 1 x 1½ inches and sinus 1½ inches deep.	20 mos.	2 mos.	Cure.
2	W., Lincolns.*	2 large surface wounds on forearm 5 x 4.	6 wks.	2 "	"
3	H. E. B., E. Surreys.	3 sinuses opening from back of scapula, each 6 inches long.	9 mos.	2 "	"
4	G. G. T.	Ulcer on end of stump.	3 "	3 wks.	"
5	M., K.O.R.L.	Wound on shoulder.	10 "	4 "	"
6	M.	Sinus in tibia 1½ inches deep.	12 "	7 "	"
7	H. D., Scots Guards.	Ulcer on instep.	2½ "	3 "	"
8	A. A. A., Canadians.	Cavity and sinus in femur, 2½ inches deep.	14 "	2 mos.	"
9	F. G. B., Grenadier Guards.	Two sinuses in leg, one 8 and one 5 inches long.	8 "	1 mth.	"
10	J. W., Grenadier Guards.	Cavity in finger after whitlow.	3 wks.	8 days.	"
11	P. V., Suffolks.	Cavity and sinus, 2 inches deep, in left humerus.	14 mos.	3 wks. & 3 days.	"
12	G. C., R. Fusiliers.	Sinus in stump after amputation.	6 "	5 days.	"
13	T. C., D.L.I.	Wound in shoulder below clavicle, leaving sinus 2½ inches deep.	4 "	16 "	"
14	Major M., R. Inniskilling Fusiliers.	Sinus in lower end of outside of R. humerus 1½ inches deep.	10 "	5 "	"
15	J. G., Seaforth Highlanders.	Ulcer in centre of amputation flap.	9 "	3 wks.	"
16	Sister N., Q.A.M.N.S.	Large opening at back of right ear following 2 operations for mastoiditis.	7 "	3 "	"
17	W. B., Lifeguards.	Suppuration of eye socket after enucleation of eyeball.	6 "	3 "	"
18	Lieut. B., R. Warwicks.	Sinus leading down to right femur, 2 inches deep.	7 "	3 "	"
19	Lieut. R., Canadian Inf.	Trench gingivitis with ulceration of gums.	3 wks.	3 "	"
20	W. M., Hants.	Sinus and abscess cavity in amputation stump.	6 mos.	5 "	"
Total ... ..			157 mos. 2 wks.	18 mos. 2 wks.	

\* In this case treatment was discontinued for four weeks.

N.B.—I have only failed in one case, Major S. H. He was twice plated for fracture of the femur. The "plate" acted as a "foreign body."

The properties of ozone, which have a wonderfully healing effect, are, as far as one can say at present, three:—

1. It is a strong stimulant and determines an increased flow of blood to the affected part.

2. It is a germicide, which destroys all hostile micro-organic growth.

3. As the French chemist Hennocque has shown, it has great powers in the formation of oxyhæmoglobin.

The ozone is applied on the wounded surface or to the cavities and sinuses for a maximum time of 15 minutes, or until the surface becomes glazed. Ozone has the particular power of disclosing dead bone, foreign bodies, septic

deposits, &c. This, I believe, it does by destroying the granulations and micro-organic growths (presumably unhealthy) that are found in close contact with septic deposits, foreign bodies, or dead bone.

## Cleansing and Dressing.

Wounds and sinuses, &c., are washed twice daily with boiled water and a dressing of dry gauze is applied. It must be observed that at first ozone causes an increase of the discharge of pus; later on the pus is replaced by clear serum, which at a still later stage becomes coloured reddish or pinkish. In open wounds it is necessary to strip off the parchment-like film surrounding the edges, which is composed of oxidised serum. This is easily effected by applying a hot compress for 15 or 20 minutes, after which the film can be easily peeled off with a dissecting forceps.

At present our knowledge of the effects of ozone is but small, but later I hope to bring before the medical public further satisfactory facts with reference to its working and results.

## Clinical Notes:

### MEDICAL, SURGICAL, OBSTETRICAL, AND THERAPEUTICAL.

#### PLACENTA PRÆVIA AND CÆSAREAN SECTION.

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ONE meets only a few cases of placenta prævia in which the condition of both mother and child justifies the operation of Cæsarean section. This is more especially so in hospital practice, where such patients are usually admitted in a more or less advanced stage of labour and only after there has been a considerable loss of blood, a state of affairs which would obviously contra-indicate a major operation when other means of delivery are open to us.

In recent years it has been recognised that the best treatment for certain cases of placenta prævia is Cæsarean section, and the results obtained among these carefully selected cases have been very satisfactory both as regards the maternal mortality and that of the infants. The maternal mortality of placenta prævia treated on the ordinary lines is 4 to 8 per cent., and the average foetal mortality is 60 per cent. Munro Kerr says: "The best figures give 4 per cent. and 35 per cent. respectively, and they are as low as one can ever expect to reach with the present recognised methods of treatment." But in certain cases of placenta prævia, such as the one described below, Cæsarean section would, I think, justify us in expecting much better results than a maternal mortality of 4 per cent. and a foetal one of 35 per cent.

As regards the mothers, there seems no special reason why Cæsarean section performed in suitable cases of placenta prævia should not yield quite as good results as it does in cases of contracted pelvis, when the operation is performed under the best conditions, the maternal mortality then being 2·9 per cent. (Amand Routh). Berkeley and Bonney place the maternal death-rate of Cæsarean section, when this operation is performed under the best conditions, as "probably under 1 per cent." In well-selected cases of placenta prævia the maternal mortality should not, therefore, be greater than about 2 per cent., i.e., about half as great as we could expect from any other method of treatment. One other great advantage to the mother is a lesser risk of morbidity as compared with that which results from the necessary manipulations, often prolonged, which accompany delivery *per vias naturales*.

The foetal mortality must obviously be very greatly reduced by Cæsarean section, and the rate of 35 per cent. at the best would be reduced to one of about 5 per cent. Further, in most cases the mother should be as well able to nurse her infant as after normal delivery, a result which, because of some slight sepsis or as the result of hæmorrhage before and during delivery, is often denied to the mother who has been otherwise delivered.

Generally speaking, the operation of Cæsarean section in a case of placenta prævia is indicated under the following