onset of anginal attacks, and other disturbances in the night can be readily accounted for; also sudden death, probably due to ventricular fibrillation in most instances.

In the light of these observations it is easy to understand how in certain circumstances death may come like a thief in the night to a susceptible person living with circulatory conditions that approach the danger line, though these conditions may, in favourable circumstances and barring fresh developments, be compatible with many years of moderately active life.

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AN INVESTIGATION INTO THE EFFECTS OF THE ARSENOBENZOL TREATMENT OF SYPHILIS ON LIVER FUNCTION.

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ALTHOUGH salvarsan and its substitutes and modifications have now been in general use for a considerable number of years, syphilologists are not yet in complete agreement upon the method of using these remedies in the treatment of syphilis. Some, for example, rely entirely or principally upon salvarsan as a curative agent; others deem that it should be employed in conjunction with mercury or with the new bismuth preparations. There can be no doubt, however, as to the advantages of this drug; but it is not one to be used recklessly, and of late, since its more extensive use, and since its employment in larger doses and in a greater number of injections, certain untoward results have become familiar to those working with it. Modern methods have largely succeeded in abolishing, or at least diminishing, the immediate dangers or inconveniences, such as fever; but there still remain two important and serious consequences attributable to its administration—arsenical dermatitis and jaundice. Foulerton was among the first to call attention to the possible harmful effects of the arsenical compounds on the liver, regarding fatal cases of poisoning by the arsenobenzol compounds as essentially identical with poisoning by chloroform, ether, T.N.T., and phosphorus. In his experiments carried out with arsenical compounds in rabbits he found an interstitial hepatitis with injury to the parenchyma cells, and a nephritis in addition to the hepatitis. Many other workers have adverted to the possibility of serious toxic effects on the liver tissues, and indeed it would appear that these, with dermatitis, may now be regarded as being among the most common of the ill effects following the administration of the drug.

In considering the treatment of syphilis it has clearly to be kept in mind that cure may only be expected with any degree of confidence in the earlier stages of the disease; therefore in this early stage the powerful remedies available may be pushed to the degree of tolerance with justification. The problem presented to the dermatologist is twofold: first, he has to determine what amount of arsenical compound is required to give in the early or curable stage the best chance of cure; and, secondly, having decided this, he has further to consider whether this amount can be administered without risk of injury to the individual.

To the first part of the problem attention was paid by one of us and Kennaway in an earlier series of cases, and it was found that a series of ten injections of novarsenobenzol, amounting to 8.7 grams, satisfied the requirement in most cases—provided that treatment was subsequently continued with mercury. In view of the statements by competent observers as to the possible harm to the liver tissues from such a dosage, the present investigation was undertaken.

A series of 57 patients in different stages of disease, undergoing treatment with novarsenobenzol, was investigated, the liver functions being tested by methods to be described. The facts as ascertained by us are set out briefly in Table I. It will be noted that the examinations were carried out both during and at varying intervals after salvarsan administration. This was done in order that the harmful effects, if any, could be determined not only during the period when the arsenical compound was being administered, but also at varying periods afterwards, when delayed harmful effects might occur.

The investigator of hepatic function is confronted at the outset with certain physiological facts which make evident to him the difficulty of his task. Thus, the work of F. C. Mann has shown that four-fifths of liver substance can be removed from an animal without occasioning any apparent adverse symptoms, apart from some temporary shock inevitable where so extensive an operation has been performed. If, however, more than four-fifths of liver substance be removed, the animal develops convulsions, which may be prevented, at least for some time, by the intravenous administration of glucose solution. This fact is extremely important; it corroborates the common observation that even in cases of massive secondary carcinomatous deposit in the liver the only symptom of hepatic disturbance may be jaundice. There is evidently what may be termed an enormous "liver reserve," and this prevents any known test from being entirely satisfactory, because, unless a very large amount of liver tissue be put out of action, a single test may fail to give a positive reaction. We have attempted to overcome this difficulty by using a number of different tests.

Tests of Liver Function.

The tests that may be employed to determine liver function naturally fall into certain groups which are designed to investigate particular functions. Owing to the nature of the chemical reactions in some of the tests it is often extremely difficult to read the result accurately; we have therefore selected the following as being the most likely to give reliable results. They are those depending on biliary function and those depending on the lipase content of the blood.

The first group is concerned with the investigation of bile pigments and their precursors, urobilin and urobilinogen. We may here briefly summarize the metabolism of these substances. As is well known, the liver secretes bilirubin and biliverdin into the intestines; there these pigments meet the intestinal bacteria and are by them converted into various substances, the most important, from the point of view of the tests employed, being urobilinogen. Some of this chromogen is absorbed into the blood stream, and is then picked out by the liver cells, converted into bile pigment, and re-excreted with the bile. A very little passes out into the urine. But if there be any damage to the liver cells this property of converting urobilinogen into bile pigment is lost, and therefore urobilin accumulates in the blood and is excreted in excess in the urine. Hence it follows that any excess of urobilin in the urine points to damage of the liver cells, and the demonstration of such an excess may be accepted as evidence of liver defect. This phenomenon precedes the appearance of bile pigments in both blood and urine. The details of the tests employed to detect this substance are given later.

The tests depending on the lipase content of the blood are based upon observations by Whipple, who showed that after chloroform poisoning the lipase concentration of the serum rose, and that this increase could be prevented if the liver was "cut out" of the circulation. He suggested the estimation of blood lipase as a test of hepatic function, and this method has been used in this country in especial by Mackenzie Wallis.

The technique employed in the different tests is as follows:

Tests for Urobilin and Urobilinogen.

Ehrlich's aldehyde reaction: To 5 c.cm. of urine two drops of a 3 per cent. solution of paradimethylaminoazobenzaldehyde in 50 per cent. HCl are added. If the test be positive, the resulting mixture becomes deep red. Occasionally it is necessary to warm the solution to bring about the reaction. This test.

TABLE I.

Case No.	Sex.	Age.	Total N A.B. (Grams).	Interval between First Injection and Test.	E. A.	U.	H.	I.	Gm.	F.	L.	Condition.
163	F.	22	6.6	4 years 8 months	—	—	—	—	—	—	—	Secondary syphi is.
392	F.	25	12.45	4 years	—	—	—	—	—	—	—	Secondary syphilis.
529	M.	37	9.3	2 years 2 months	—	—	+	—	—	—	—	Eleven years' duration.
699	M.	26	6.3	2 years 8 months	—	—	—	—	—	—	—	Secondary syphi is.
723	M.	21	21.9	2 years 6 months	—	—	—	—	—	—	—	Secondary syphilis.
778	F.	24	7.8	2 years 3 months	—	—	—	—	—	—	—	Jaundice previously.
859	F.	54	9.0	2 years 2 months	+	±	+	—	—	±	+	Syphi itic cirrhosis of liver.
935	F.	24	16.5	2 years	—	—	—	—	—	—	—	Late secondary syphilis.
911	M.	23	13.2	2 years	—	—	+	—	—	±	—	Secondary syphilis.
926	F.	17	11.65	2 years	—	—	—	—	—	—	—	Congenital syphi is.
1024	M.	24	6.0	1 year 9 months	—	—	—	—	—	—	—	Arsenical dermatitis after seventh injectio
1019	M.	25	12.9	1 year 8 months	—	—	—	—	—	—	—	O d-standing syphilis.
1089	F.	28	13.5	1 year 7 months	—	—	+	—	—	—	—	Old standing syphilis.
1148	M.	40	7.8	1 year 5 months	—	—	—	—	—	—	—	Erythema after ninth injection.
1171	F.	25	1.2	1 year 4 months	—	—	—	—	—	—	—	Slight erythema after second injection.
1183	F.	51	8.7	1 year 3 months	—	—	—	—	—	—	—	Old-standing syphilis.
1189	M.	21	12.3	1 year 3 months	—	—	—	—	—	—	—	Secondary syphilis.
1209	F.	30	3.6	1 year 2 months	—	—	—	+	—	—	—	Three years old syphilis.
1219	M.	46	6.15	1 year 2 months	—	—	—	—	—	—	—	O d-standing syphilis.
1232	M.	37	8.7	1 year	—	—	—	—	—	—	—	Tabes.
1236	M.	20	16.05	1 year	—	—	—	—	—	—	—	Secondary syphilis.
1239	F.	28	8.7	1 year	—	—	—	—	—	—	—	Secondary syphilis.
1251	M.	45	7.8	1 year	—	—	+	—	—	—	—	Jaundice 6 months before tests.
1284	F.	38	6.9	1 year	—	—	—	—	—	—	—	Old-standing syphilis.
1299	M.	53	12.9	11 months	—	—	—	—	—	—	—	Primary syphilis.
1316	M.	29	8.7	10 months	+	±	+	—	—	±	±	Slight jaundice.
1330	M.	26	11.1	10 months	—	—	—	—	—	—	—	Secondary syphilis.
1363	F.	55	0.45	8 months	—	—	—	—	—	—	—	Tertiary syphilis.
1391	M.	42	1.5	7 months	—	—	—	—	—	—	—	Slight dermatitis after second injection
1396	M.	24	7.05	6 months	—	—	+	—	—	—	—	Secondary syphilis.
1398	F.	30	7.8	6 months	—	—	—	—	—	—	—	Secondary syphi is.
1401	F.	42	6.6	6 months	—	—	—	—	—	—	—	Secondary syphilis.
1408	F.	13	3.85	6 months	—	—	—	—	—	—	—	Congenital syphi is.
1417	F.	24	8.4	6 months	—	—	—	—	—	—	—	Secondary syphilis.
1413	F.	23	6.0	6 months	—	—	—	—	—	—	—	Secondary syphi is.
1414	F.	31	7.2	6 months	—	—	+	—	—	—	—	Late secondary syphilis.
1415	F.	23	7.5	6 months	—	—	+	—	—	—	—	Syphi is of 4 years' standing.
1418	M.	29	6.3	5 months	—	—	+	—	—	—	—	Late secondary syphilis.
1420	F.	22	7.8	5 months	—	—	—	—	—	—	—	Pregnant. No jaundice.
1430	F.	32	5.85	5 months	+	+	+	—	—	—	±	Secondary syphilis.
1434	M.	35	5.7	4 months	—	—	—	—	—	—	—	Secondary syphilis.
1435	F.	20	8.4	4 months	—	—	—	—	—	—	—	Secondary syphilis.
1454	F.	34	5.4	4 months	—	—	+	—	—	—	—	Tertiary syphilis.
1455	F.	34	5.85	4 months	—	—	—	—	—	—	—	Secondary syphilis.
1456	M.	23	4.5	3 months	—	—	—	—	—	—	—	Primary syphilis.
1457	M.	43	6.0	3 months	—	—	—	—	—	—	—	Tertiary syphilis.
1459	F.	22	6.0	3 months	+	±	+	—	—	—	—	Arsenical dermatitis.
1478	F.	18	5.45	3 months	—	+	+	+	+	+	+	No jaundice. Congenital syphilis.
1479	F.	28	4.75	3 months	—	—	—	—	—	—	—	Secondary syphilis.
1485	M.	49	0.6	2 months	—	—	—	—	—	—	—	General paralysis of the insane.
1487	M.	53	6.95	2 months	—	—	—	—	—	—	—	Old-standing syphi is.
1490	M.	34	5.25	1 month	—	—	—	—	—	—	—	Tabes. Jaundice 6 months later.
1494	F.	32	4.8	2 months	—	—	—	—	—	—	—	Secondary syphilis.
1495	M.	41	1.05	1 month 2 weeks	—	—	—	—	—	—	—	Tertiary syphilis.
1497	M.	53	1.12	14 days	—	—	+	—	—	—	—	O d-standing syphilis.
1498	M.	42	0.6	14 days	—	—	—	—	—	—	—	O d-standing syphilis.
1508	M.	54	None	—	+	+	+	—	—	—	—	Old-standing syphilis.

Key to Tests Employed.—E.A.=Ehrlich's aldehyde; U.=urobilin; H.=Hay; I.=iodine; Gm.=Gmelin; F.=Fouchet; L.=lipase.
+, Positive; —, negative; ±, doubtful.

when positive, demonstrates the presence of a pathological amount of urobilinogen.

Schlesinger's test for urobilin: 20 c.cm. of urine is acidulated with acetic acid and then the urobilin is extracted by inverting with 5 c.cm. of amyl alcohol. The amyl alcohol layer is pipetted off and a few drops of a 10 per cent. alcoholic solution of zinc chloride are added to it. If a green fluorescence develops the test is positive; in addition the characteristic spectrum can be observed. A positive reaction demonstrates an excess of urobilin.

For the detection of bile pigments and salts the familiar—but unreliable as regards our special purpose—Gmelin's, Hay's, and iodine tests were employed.

Tests for Bile Pigment in the Blood.

To demonstrate the presence of these substances we have employed Fouchet's test. This reaction is extremely delicate, but nevertheless very simple to perform. To three drops of serum three drops of the following solution are added: 5 grams trichloracetic acid, 20 c.cm. H₂O, 2 c.cm. FeCl₃ solution (10 per cent.). A white precipitate appears at once and if bile is present the precipitate so formed becomes greenish-blue, reaching its maximum degree in twenty minutes. It is claimed by the originator of this test that it is capable of giving a positive result in so high a dilution as 1 in 60,000. Our observations have confirmed its extreme delicacy and reliability.

Blood Lipase Estimation.

We employed the method of Lowenhardt. Into four test tubes 1 c.cm. of serum is placed, together with 0.3 c.cm. of toluene to prevent decomposition; 3 c.cm. of water are then added to each tube, making the total volume 4 c.cm. To two of the tubes 0.26 c.cm. of ethyl butyrate is added, and all four tubes are incubated for eighteen to twenty-four hours in an

incubator at 37° C. At the end of this time the tubes are removed, and a drop of azolitmin solution is added to each. The tubes containing serum alone are alkaline, and are titrated with N/10 acid. The other tubes, in which the lipase will have produced butyric acid, are acid in reaction, and are consequently titrated with N/10 alkali. The amount of lipolytic action is the sum of the mean amount of acid and alkali used. Normally, this is between 0.2 and 0.3 c.cm.

To be of value as evidence, any series of tests must satisfy two criteria: they must singly or in combination be capable of returning positive results when the defect they claim to demonstrate is present; at the same time they must be of such a nature that they do not give positive evidence where normal conditions exist.

Hay's, the iodine, and Gmelin's tests failed to satisfy the standard of accuracy aimed at. On the other hand, we believe that Ehrlich's aldehyde test, Schlesinger's test, Fouchet's test, and the lipase test are trustworthy, as shown by the following investigations undertaken to test their reliability.

Negative controls were made on a series of sixteen students, and also on sixteen patients who had been admitted to hospital for conditions which did not involve the liver, and in whom, therefore, the liver functions might be assumed to be normal. In every case the tests as applied to the urine and blood gave negative results. This series of 32 cases indicates that the tests are so far reliable in that they do not give positive results where the liver is functioning normally.

The group of positive controls demands fuller consideration; details are given below.

CASE I.—C. A., female, aged 50 years, under the care of Dr. Essex Wynter. On admission the patient was jaundiced and presented a palpable mass in the left hypochondrium. All tests strongly positive. *Post-mortem* examination confirmed the diagnosis of a carcinoma of the gall bladder.

CASE II.—Mrs. S., aged 60 years, under the care of Dr. Wynter. On admission slight jaundice, with enlargement of the liver. A diagnosis of cirrhosis of the liver was made and verified *post mortem*. Here all the reactions were positive.

CASE III.—F. B. (under the care of Dr. Izod Bennett). The patient was a heavy drinker and presented the signs of alcoholic cirrhosis with enlarged liver. All reactions positive, except Gmelin and iodine tests. Lipase 0.6.

CASE IV.—H. R., aged 29 (under Dr. Cockayne). Enlarged liver; no jaundice. All reactions positive except Gmelin's and iodine tests. Lipase 0.5. Diagnosis, early cirrhosis.

CASE V.—H. N., aged 22 (under Dr. Cockayne). Jaundice started when 15 and has continued. No symptoms. Liver enlarged. Fragility of corpuscles increased. Clinical diagnosis, Hanot's cirrhosis. All reactions positive. Lipase 0.7.

CASE VI.—H. B., male, aged 8 (under Dr. Bennett). Three weeks before admission this child had acute catarrhal jaundice, but jaundice had practically disappeared when tests made; a slightly enlarged liver could be detected. All reactions positive. Lipase 0.5.

CASE VII.—E. H., female, aged 65 (under Mr. Sampson Handley). Jaundiced when admitted and distended gall bladder. At this stage all reactions were positive. After six weeks the jaundice and gall bladder distension had disappeared. All reactions were again positive at this stage except the iodine and Gmelin tests. Lipase 0.4.

CASE VIII.—Male, aged 14 (under Dr. Bennett). Patient had severe indigestion and "felt ill." All reactions positive except the iodine and Gmelin's reactions. A week later the patient developed acute catarrhal jaundice. Lipase 0.5.

These eight positive controls are summarized briefly in Table II.

TABLE II.—Positive Controls.

Case No.	Summary.	BLOOD.		URINE.					
		Fouchet.	Lipase.	Ehrlich Aldehyde.	Urobilin.	Iodine.	Hay.	Gmelin.	
1	Carcinoma of gall bladder; jaundice	+	0.6	+	+	+	+	+	
2	Cirrhosis; slight jaundice	+	0.5	+	+	+	+	+	
3	Fatty infiltration; early cirrhosis (?); no jaundice	+	0.6	+	+	—	+	—	
4	Early cirrhosis; no jaundice	+	0.5	+	+	—	+	—	
5	Hanot's cirrhosis	+	0.7	+	+	+	+	+	
6	Acute catarrhal jaundice	+	0.5	+	+	—	+	—	
7	Biliary obstruction; jaundice	+	0.4	+	+	+	+	+	
8	Acute catarrhal jaundice	+	0.5	+	+	—	+	—	

We may now proceed to the examination of the series of 57 cases of syphilis where salvarsan had been administered and where the liver functions were investigated by the methods already detailed. Table I summarizes the type of case, the amount of arsenical compound administered, the interval after commencing treatment when the liver functions were investigated, and the results obtained from the investigation. Four different groups may be identified: those where dermatitis occurred; those where jaundice developed; those where chemical evidence of liver defect was shown by the tests (without clinical manifestations); and those where the liver functions appeared to be normal. The last group, as will be seen, includes the majority of cases.

Arsenical Dermatitis.

In this group are included five cases—1024, 1148, 1171, 1391, and 1459. Several observations may be made in respect of this group.

No. 1024 developed severe dermatitis after the seventh injection. The Wassermann reaction had become negative after the fourth injection, was again found negative, but became positive one year after the commencement of treatment and has remained positive up to the present date in spite of most vigorous treatment. One year and nine months after beginning treatment all the liver tests were negative. This patient made a complete recovery from his cutaneous disturbance.

No. 1148 developed dermatitis of moderate degree after the ninth injection, from which he completely recovered. The Wassermann reaction became negative after the fifth injection and remained negative for six months; it then became positive and has remained positive in spite of continued mercurial injections carried on for some months. In this case the liver functions were investigated

one year and five months after treatment began and were all negative.

No. 1171—a female, aged 25 years, with congenital syphilis—received two injections of novarsenobenzol. She then developed an erythema. Treatment was continued with mercury. Here also the Wassermann reaction at first became negative but relapsed later to a positive phase. The liver functions were investigated one year and four months after the first arsenical injection and were then completely negative.

No. 1391 developed dermatitis after the second injection; there was complete recovery from this. The Wassermann reaction became negative seven months later. Seven months after commencement of treatment all reactions for liver function were negative. The subsequent history of this patient is not known.

No. 1459 developed severe dermatitis after the seventh injection of novarsenobenzol. She absented herself from the hospital for eighteen months. On returning the Wassermann reaction was found to be negative. In this case the liver function was investigated three months after the beginning of treatment and gave positive results.

These five cases present certain interesting features. It will be seen that in three out of the five the Wassermann reaction became ultimately positive—an observation contradicting the general statement that where dermatitis occurs a continued negative Wassermann reaction is the rule. In only one case was evidence of disturbed liver function obtained, and it is noteworthy that in this case the investigations were made at the shortest interval after the administration of the arsenic. It would seem, however, that even if a disturbance of the liver is associated with dermatitis, such a disturbance is of a temporary nature and is followed by complete recovery of function.

It will be noted that in these cases the total amount of arsenical compound (novarsenobenzol) varied considerably. The cases in which severe dermatitis developed (1024 and 1459) each received 6 grams. On the other hand, dermatitis of moderate severity followed doses of 7.8 and 1.5 grams (1148 and 1391). It would therefore appear that the degree of dermatitis does not entirely depend upon the amount of the drug administered; indeed, the dosage in these cases is less than that given to the average patient in the clinic, where the drug is readily tolerated. The occurrence of dermatitis in two sisters treated at different times indicates that some individual idiosyncrasy predisposes to this form of eruption.

Jaundice.

We have had the opportunity of testing the liver functions in five instances where jaundice followed the administration of novarsenobenzol. The tests were carried out at varying periods after the jaundice had manifested itself. The actual details may be summarized as follows:

No. 778, a female, aged 24 years, received 7.8 grams in ten injections with subsequent mercurial treatment. Twelve months after beginning treatment the patient developed a mild type of jaundice from which she made complete recovery. Three months later the liver functions were tested and were all completely negative. In this case cure of the syphilitic infection would appear to have been effected, for the Wassermann reaction was negative two years and three months after first coming under observation.

No. 1209, a female, aged 30 years, received 3.6 grams of novarsenobenzol in six weekly injections. Jaundice developed five months after the first injection. All the liver tests, except Hay's, were negative eight months later. The patient was probably cured, for the Wassermann reaction has remained negative, and a healthy child was born at the end of treatment.

No. 1251, a male, aged 45, suffering from tabes, received 7.8 grams of novarsenobenzol in ten weekly injections. He developed jaundice six months after the last injection. Here also all the liver tests were negative one year later—with the exception of Hay's test.

No. 1316, a male, aged 28 years, received 8.7 grams in ten weekly injections. Slight jaundice developed eight months after the first injection. In this case the liver tests were investigated while jaundice was still present and gave positive results (see Table I). It may be assumed that the syphilitic infection was cured in view of a series of negative Wassermann reactions obtained.

No. 1490, a male, aged 34 years, with tabes and a Charcot joint of the right ankle, received 5.85 grams of novarsenobenzol. He developed jaundice six months after the first injection. Here the liver tests were carried out after the third injection—that is, before the jaundice appeared—and were then completely negative. At this time, therefore, the liver functions were apparently normal. A complete recovery was made from the jaundice and an improvement also occurred in the tabes.

Jaundice is the most obvious and therefore the most frequently observed evidence of disorder of the liver following the administration of salvarsan compound. But apart from this very obvious indication of a derangement of the hepatic function, it is possible for a disturbance to occur

without jaundice. Such a defect can only be determined by special tests—for example, those we have already described in detail. While the incidence of jaundice may be used to indicate the degree of hepatic derangement from the arsenical substances, we believe better evidence can be obtained by employing special chemical tests for liver efficiency. All the tests used, as has been pointed out, were submitted to careful preliminary investigations, and these controls showed that Ehrlich's aldehyde, the urobilin, Fouchet's, and the lipase content tests could be relied upon; therefore deductions may be based upon the results obtained from these tests.

CONCLUSIONS.

If the series of cases investigated be now examined, it will be seen that out of a total of 56* cases, where arsenical preparations had been given, in 52 the chemical reactions indicated that the liver tissues at the time the tests were made were functioning normally. Since the derangement of liver function, if any, may arise during the administration of salvarsan, or at varying periods afterwards, it is of importance that any series of tests be made at different times. This has been done, and it will be noted that the range extends from four years and eight months through gradually shortening intervals down to a period when the tests were made while the patient was actually under arsenical treatment. These investigations go to show that the salvarsan preparation used, given in the doses indicated, does not cause either immediate or late damage to hepatic tissue except in a small proportion of cases. It should not be inferred that the proportion of jaundice met with in the clinic is 5 out of 56. Examples of jaundice are rare, and we were fortunate in obtaining these while the investigations were being carried out.

There is now an extensive literature on the subject of what may be called arsenical jaundice. So striking and suggestive a phenomenon as jaundice could not escape notice, but it is open to question whether the arsenical preparations used should be held entirely or generally responsible for the condition observed. Jaundice, and even acute yellow atrophy, were noted in connexion with syphilis long before arsenic was employed in the treatment of this disease. This is very fully dealt with in the admirable report of the Salvarsan Committee of the Medical Research Council on the toxic effects following the arsenobenzol preparations. There will be found among other records that of Lasch (1894), who noted 49 cases of jaundice in early syphilis, including one where acute yellow atrophy supervened; that of Wickham Legge of 100 cases of acute yellow atrophy, 8 of which were known to be syphilitic; that of Parkes Weber (1909) recording acute yellow atrophy in a case of recent syphilis; and others similar. There is thus abundant evidence that every degree of jaundice, and even acute yellow atrophy, may occur in syphilis as an accident of this disease, and therefore may be in no way connected with the use of an arsenical preparation.

In view of these facts many hold that the jaundice observed in syphilis, whether following salvarsan administrations or otherwise, should be attributed to a special effect of syphilis on the liver. There are, however, two facts of general acceptance which appear to challenge the complete acceptance of such a hypothesis. The first is the well known observation that the administration of arsenic for various conditions in individuals free from any syphilitic taint may be followed by jaundice; the second is concerned with the occurrence of groups of cases of jaundice or acute yellow atrophy in seeming epidemic form among patients being treated for syphilis with arsenical compounds. In the latter case the suggestion has been made that some additional infection is present and that persons suffering from syphilis are especially liable to infection of this kind. But even allowing full value to these observations, it can nevertheless be maintained from the evidence we have given that the arsenical substances may be safely employed in full doses without any considerable chance of causing temporary or permanent damage to the liver tissues. In this connexion four cases may be cited.

The first, No. 1508 in our series, a male aged 54, with old-

* It will be observed that in one case where liver functions were investigated (No. 1508) no arsenic was given.

standing syphilis, gave positive evidence of liver defect (see Table I), and yet in his case no salvarsan had been given. It is easy to see that had this man been treated with arsenic the condition discovered would improperly have been attributed to the drug used. Further, if salvarsan is as harmful to liver tissue as is sometimes alleged, it might be expected that where hepatic disease is already present the administration of the drug would produce some pronounced harmful effect. The following cases contradict such an assumption. No. 859, a female, aged 54, came to the hospital in 1918 with an enlarged and irregular liver diagnosed as syphilitic. She gave a history of several attacks of jaundice, there were scars about the region of the knees, and the Wassermann reaction was positive. This woman received 9 grams of novarsenobenzol in ten injections, following which the liver ceased to be palpable, and she made progressive improvement. Chemical investigations of the hepatic functions two years and two months after treatment had been commenced gave positive results (see Table I), although the patient's general condition still remained good. No. 1315 is an example of a similar kind. This patient, a female, aged 33 years, was admitted to a medical ward with the diagnosis of syphilis of the liver; the Wassermann reaction was positive and the liver was considerably enlarged. She received 5.85 grams of novarsenobenzol, and six months after the first injection the liver could no longer be felt. The third case is an example of jaundice during the early secondary period. The patient, a female aged 20 years, presented herself with marked jaundice and secondary syphilis. In spite of this she was given a first injection of 0.3 gram of novarsenobenzol, following which the temperature rose to 102°, the febrile period lasting some days. The hepatic region was tender and the liver was noted to extend downwards some three or four inches below the costal margin. Ten days later the liver appeared to have regained its normal size and a second injection of 0.3 gram of novarsenobenzol was given. This produced further fever, but of lesser degree; the liver again became enlarged and tender. A fortnight later a further injection of 0.3 gram was given. The jaundice had by now almost entirely disappeared, and from this time the patient made satisfactory progress.

While admitting that jaundice may result from the injection of any form of arsenic and apart from syphilis, and also that there is some evidence of the occurrence of epidemic jaundice among patients being treated for syphilis—which may point to some additional unknown factor—we are nevertheless of the opinion that, in the type of jaundice met with in the clinic where our observations have been made, the condition should rather be attributed to the disease than to the remedy used. Thus we have been unable to confirm the findings of others that a disturbance of liver function is common after arsenical administration; indeed, our observations lead us to take a contrary view. Further, it has been noted by us that in a number of cases where jaundice supervened during treatment, although the result of treatment might appear entirely satisfactory, after an interval the Wassermann reaction, which may have been, and usually was, negative, again became positive, indicating that sterilization had not been complete. It may reasonably be supposed that in these cases certain spirochaetes had escaped and had assumed a special activity in the liver substance, first producing jaundice and later the positive Wassermann reaction. It would appear certain that the incidence of jaundice among those suffering from syphilis is now higher than formerly. This may, however, be explained on the assumption that in consequence of the rapid destruction of the infecting parasites by the specific remedy those natural processes of protection which would normally be called into being are not elaborated, and thus any escaping micro-organisms find the tissues they invade in an unprotected state. This would account for the phenomenon noted—that is, jaundice. It is interesting to recall that in the early days of the use of "606" the remedy was blamed for the lesions of cranial nerves then not infrequently observed, but that later it was shown that these effects were the result of the disease, not of the remedy employed to treat it.

These investigations were undertaken with an entirely open mind. The object was to determine whether the

Remarks.—In Experiment 1 there was the usual lowering of blood sugar. Experiment 2 showed definite but not such marked lowering of blood sugar. In Experiment 3 the blood sugar rose in the ordinary way. In Experiment 4 oral insulin had no effect; an evening dose of 20 units insulin was ordered instead of 15 units. In Experiment 5 oral insulin after food had no effect. In Experiment 6 oral insulin in 40 per cent. alcohol had no effect; subcutaneous insulin produced the usual lowering.