the other hand no evidence is forthcoming that the occurrence of pleural effusion or empyema is thereby made more likely. There is statistical evidence, however, that the treatment does lessen the liability to spread of consolidation to the opposite lung.

To summarize, Felton's serum, while of proved value, cannot like anti-diphtheritic serum be called a 100 per cent. remedy, and does not benefit every case. Its use does not replace the necessity or diminish the importance of general measures of treatment, and requires throughout, care and judgment. Its exhibition in severe early cases of Type 1 and 2 adult pneumonia is fully justified and frequently attended by the most gratifying results.

**ARSENCAL JAUNDICE.**

**BY HUGH GORDON, M.C., M.R.C.P.**

The question of arsenical jaundice is still very much in the melting pot. This is scarcely surprising when one remembers that the ætiology of catarrhal jaundice is still unknown; likewise that of acute yellow atrophy of the liver. Similarly, the whole question of the arsenical treatment of syphilis appears to get more controversial every day. The high hopes of the sterilizatio magna of Ehrlich gave way to steady confidence in the results obtained during the Great War with the scope of treatment in bulk which it offered. But to-day we find some who say that arsenic is dangerous unless it is given in adequate doses and over an adequate period, as it tends to create an arsenic-resistant organism. The interpretation of what is adequate in both instances varies, one need hardly say, within very wide limits. Again, there are others who are gloomy of the whole future of arsenic. For instance, in Professor Dubreuilh's words: "In the treatment of syphilis the arsenical compounds are much worn out after twenty years, whereas, after four hundred years, mercury is still holding its ground."

Now the question of jaundice occurring during treatment is of relatively small moment compared with the cure of syphilis. It is, in fact, believed by some to be identical in the majority of cases with catarrhal jaundice, and can therefore be dismissed as a mere incident, having no bearing on the serious business in hand. Since, however, what are believed to be toxic cases are reported, the catarrhal school, if we may so designate them, would abstain from giving further arsenic during the continuance of the jaundice.

The school, at the other extreme, regard any case of jaundice during the administration of arsenic with extreme disquietude, fearing it to be a toxic effect of the arsenic or one of its component radicals, and would advise against any further administration of the drug, at any rate for a long period.

In between the two extremes are varying shades of opinion, which vary from placing the blame on the syphilis alone to others who blame the combination of the factor arsenic plus syphilis, or, again, to three factors, arsenic plus syphilis plus something else.

It is a problem, then, on account of the varying unknown factors quite dissimilar to arsenical dermatitis. The exact ætiology of this is also unknown, but it lends itself to fairly precise management. It can be considered as an act of God or, more medically speaking, personal idiosyncrasy. Unless premonitory signs are disregarded, it reflects no discredit on the treatment, and is more or less independent of the dose of arsenic. It has no connection with the syphilis; at least, this view is no longer seriously considered.
For the future, no more arsenic must be given as the idiosyncrasy, once acquired, lasts for life.

None of these constants are to be found in arsenical jaundice. Its connection with the amount of drug used and with the syphilis are hotly disputed; similarly, its significance at the time and for future treatment.

A study of the various cases reported, together with the explanations attached, makes it seem fairly certain that the jaundice has not a uniform aetiology. In some cases it would appear to be caused by the syphilis primarily, though it is difficult to explain the exact mechanism—in others toxic—whilst many can be fitted into any category. What is disturbing, however, is that many fatal cases are recorded, death being usually due, but not always, to acute yellow atrophy. The first symptom has often been simply jaundice. Now there does not seem to be any general accord as to when one may suspect a serious outcome on clinical grounds, or from the relationship of the jaundice to the treatment by arsenic.

This ignorance is highly inconvenient. If, through fear of pushing a case of jaundice into acute yellow atrophy, arsenic is withheld for long periods, then the treatment of syphilis is continued under a disadvantage: at any rate, in the light of our present knowledge, since arsenic is held to be the most potent of the three great anti-spirochaetal remedies.

There is a good deal of evidence accumulating which would lead one to believe that such jaundice is comparatively rarely of toxic origin, but no golden rules exist as yet which can be consulted with regard to any given case.

Again, some cases must be regarded unequivocally as syphilis, which makes the situation particularly embarrassing. Whether they are caused by a recurrence of the syphilis in the liver in insufficiently treated cases or through interrupted treatment matters little. They obviously need further anti-syphilitic treatment of a more vigorous nature. Since in some of these cases death has been recorded at the post-mortem findings as due to the syphilis, they present the most knotty problem of all in that by withholding treatment death may be caused, as it were, by neglect.

Before studying the various theories in detail, it would be well to examine such facts as appear to have been established by various investigators from the various countries. Ruge[1] in Germany reports on a series of 736 cases occurring in the German Navy during the years 1919-29. From France come reports by Milian[2] on 119 cases during a period unspecified up till 1928. Short series are presented by Sezary[3] and Lortat, Jacob[4]. Filiol[5] reviews 102 cases up to 1931. Finally, I have attempted to investigate 104 cases occurring at St. George's Hospital V.D. Clinic during the years 1921-31.

**Percentage Incidence.**

This is said to vary by Filiol in the previously-published figures from 2 per cent. (Milian) to 20 per cent. (Du Jardin). In our series it was just over 4 per cent. In Ruge's series, which is, I think, the most important from the statistical point of view, in that his figures are the largest and his patients all under control, it was 19 per cent.

**Seasonal Variation.**

The St. George's cases are comparatively few and spread out over a number of years, which makes this investigation difficult. As far as could be established, no seasonal
incidence existed, nor did the cases appear in groups. It is not referred to by any others, so presumably it has not been noted.

**Yearly Incidence.**

In the St. George's series, the yearly percentage was above normal in 1921-22; remained roughly constant for the next five years, and appears to be gradually increasing up to date. So far as one can judge from such small figures, the condition is, if anything, not getting any rarer.

Ruge has charted his yearly incidence together with that of ordinary catarrhal jaundice, and finds that the two curves, though varying considerably from year to year, are very closely parallel.

**Sex and Age.**

In the St. George's series there were twice as many men as women, which is roughly equal to the total numbers treated. There were twice as many cases occurring in those under 40 than in those over that age. Unfortunately, the total numbers treated of the two age-groups was not obtainable, so this finding is not of much value.

Filiol points out that in the great majority of his cases jaundice supervened in young subjects who had had a clean bill of health previously as regards their liver.

**Relationship of Jaundice to Previous Treatment.**

Firstly, cases are recorded which have occurred in non-syphilitics treated with arsenic. Filiol gives a percentage of 1-75 per cent. as opposed to 7-5 per cent. in syphilitics treated. His figures for the non-syphilitics are, however, only based on one case and do not therefore mean very much. Ruge finds that non-syphilitics treated with arsenic furnish 0-7 per cent. of his total cases.

Secondly, jaundice occurs in cases treated with bismuth and mercury. In the St. George's series there were two cases who had not received arsenic for six months, and who developed jaundice, one after a course of bismuth and one during it. Ruge quotes cases treated by bismuth alone as furnishing 0-13 per cent. of his total. Milian, out of 105 cases, has seven cases occurring during administration of mercury and two cases during administration of bismuth. Milian's treatment, however, is usually by means of alternating and not combined courses, so that these may well be regarded as occurring after the preceding course of arsenic. He has, however, three cases occurring after.

Milian records ten cases of jaundice occurring as a secondary symptom of untreated syphilis, which were treated solely by N.A.B. and recovered quickly.

So far, then, we can allow that arsenic alone has produced jaundice in the absence of syphilis, also that syphilis can produce it without arsenic. Bismuth plus syphilis is very occasionally guilty, but by far the most usual predisposing cause is arsenic plus syphilis.

With regard to the quantity of arsenic used and the incidence of jaundice, Colonel Harrison states: "Further, there is undoubtedly, though this is denied by some writers, a direct connection between the intensity of treatment and the incidence of jaundice." Bodin and Brodier have published figures which tend to confirm this impression. In a series where the total amount of N.A.B. given in a course was under
4 gr., the percentage of jaundice is 2.4. When the total dose was between 4 and 5 gr., the percentage incidence was 4.8; over 5 gr. the percentage was 5.7.

Milian, on the other hand, stoutly maintains that insufficient doses of arsenic are particularly apt to cause the type of jaundice which he regards as a hepato-recidive.

The Relationship between the Arsenic and the Appearance of the Jaundice.

Here the St. George's figures are remarkably in accordance with those of Ruge and Milian, but not of Filiol. Eighty per cent. of the St. George's cases occurred after a course of treatment. For the sake of clarity, these will be called post-therapeutic, as opposed to those occurring during treatment, which will be called inter-therapeutic. Obviously those cases occurring only a fortnight after the termination of a course are on the borderline. This does not, however, alter the very heavy preponderance of the post-therapeutic incidence, for the maximum appearance of the jaundice was between two and three months after a course, the actual figures were:—

<table>
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<tr>
<th>1-14 days</th>
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<td>5</td>
<td>15</td>
<td>17</td>
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Total—84

Seventy-five per cent. of Milian's cases were post-therapeutic, only his greatest incidence was at one month.

Ruge found that 87 per cent. of all cases occurred within three months of the termination of the course, the maximum incidence being about six to eight weeks after the end of the first course; in the St. George's series, 62 out of the 84 cases referred to after the first course. Filiol, on the contrary, found 50 per cent. of his cases were intra-therapeutic, the actual figures being: 57 during the course, and 27 within the first month.

An unpublished personal communication from the Salford Municipal Clinic rather curiously tends to confirm this post-therapeutic tendency. The treatment in force there consists of eight weekly injections of N.A.B., each 0.6 of a gramme, totalling therefore 4.8 gr., which are followed without any rest by six weekly injections of bismuth. These alternating courses are continued for 34 weeks without a break. Over a given period, 20 per cent. of the total cases of jaundice were noticed to occur at the fifteenth week of treatment and a further 25 per cent. at the 16th. Thus, nearly 50 per cent. of his total incidence occurs seven to eight weeks after the termination of the first course of arsenic. It is a point of very considerable interest to notice that in these cases this has occurred, although there has been no rest interval, and the treatment continued throughout the interval with bismuth.

During most of the period of the St. George's cases, the regulation rest interval after the first course was three months, part of which time the patient was on iodine. The first course has varied, both in the quantity and quality of arsenic used during various periods, but it would be accurate to say that it has never exceeded 5 grm. of N.A.B., and has often been below that. It has always been a mixed course lasting from seven to nine weeks, consisting of a simultaneous injection of an arsenical compound and either mercury in the earlier years or bismuth during the more recent.

The first course employed by Ruge consisted of arsenic to the total amount of 6.5 grm. and 20 c.c. of a bismuth preparation; the routine interval from the first to the second course was six weeks, and between the second and third courses, three months.
It is not quite clear then, when he speaks of the maximum incidence being six to eight weeks after the end of the first course, whether the jaundice has not occurred just after the beginning of the second course or not. The St. George's cases are, however, a pure culture, so to speak, of post-therapeutic cases.

Milian does not specify what exact methods of treatment have been adopted throughout his series, but it is probable that the courses would be alternating, and that a course of arsenic totalled 7 to 9 grm.

After very different systems of treatment, then, it appears that jaundice shows this curious tendency to appear post-therapeutically—in our series usually after so long an interval as two to three months. It seems, then, that in attempting to elucidate the problem of arsenical jaundice in general that this time lag is one of the most important elements which must be considered.

Since Milian's views are the most dogmatic and, on logical grounds at any rate, make the most convincing appeal, they will be examined at first in a little detail.

He argues that syphilis may, after a course of arsenic, recidive in the liver comparably to the neuro-recidives which have been long established. These were cured by further arsenic and so, in his opinion, are the hepato-recidives. He has the courage of his convictions, for all the seventy-nine cases of his series, referred to previously, which were post-therapeutic and regarded by him as hepato-recidives were placed on a further course of arsenic. Sixty are described as recovering quickly, eleven did not continue the treatment "owing to neglect," in only four the treatment had to be discontinued, in two cases owing to nitroidal crisis, in one haemorrhages into the skin, and in one erysipelas. In no case was the jaundice itself made worse. Further, according to him, jaundice occurring during a course of treatment may also be due to the syphilis. Here the situation is not nearly so clear. There are three possibilities. One toxic, two syphilitic, three what he calls biotropic. To make the diagnosis of toxic jaundice, he insists that other signs of arsenical intoxication are present. In the biotropic cases he regards the jaundice as being due to organisms in the liver or biliary apparatus, which have had their virulence raised by the action of the arsenic. He regards catarrhal jaundice as an example of this. In such cases further arsenic is not advisable as long as the jaundice lasts, in that it may tend to aggravate the affection. If the syphilis is at fault, during the course of treatment, the cause is relative or complete arsenic resistance, and if arsenic is to be continued it must be used in high doses or the remedy changed to bismuth or mercury.

He maintains that clinical differences exist between the various types. In catarrhal jaundice there is usually a febrile onset, vomiting and diarrhoea and a dirty tongue. In lithiasis the usual gall bladder syndrome. In the hepato-recidives the jaundice is an isolated phenomenon, the tongue is clear and there is very little disturbance in the general health. Frequently the jaundice is disassociated, i.e. bile pigments in the urine, and absence of bile salts. Another important point in clinching the diagnosis is the return of some other syphilitic phenomena such as headaches and a relapsing Wasserman reaction.

To illustrate his arguments a few cases will be mentioned from the French literature.

(1) Reported by Marcel Pinard. A man with a chancre of the tonsils and a positive W.R. was treated as follows: 5 injections of N.A.B. totalling 3·5 gr. in seven days; appearance of a rash diagnosed as "an erythema of the ninth day." Treatment
continued at the rate of 0.9 gr. per five days. At the end of seventeen days he had received 5.54 gr. The next day jaundice appeared, but as an isolated symptom, no vomiting, headaches, or signs of any intoxication. The jaundice was, however—not unreasonably, many will say—regarded as toxic, and treatment was suspended. After a week the jaundice was unaltered, the W.R. ++, and what was suspected as syphilitic fissures appeared on the lips. Thus, ten days after the appearance of jaundice, arsenical treatment was recommenced with a dose of 0.9 gr. No ill-results, in fact the jaundice started to fade and the lesions on the lips to heal. Treatment was continued, but with a dose of 1.05 gr. every day. The W.R. taken after 3 more injections was negative, and the jaundice practically gone.

(2) Also reported by Pinard. A secondary syphilitic given three injections of "606" 0.1 gr., 0.2 gr., and 0.3 gr. There was then no treatment for three weeks on account of influenza, after which time the patient became acutely ill with a sudden attack of jaundice, vomiting, amblyopia—diagnosis, syphilitic hepatitis and meningitis partially caused by interrupted treatment. Treatment was instituted by N.A.B., starting with 0.1 gr., rising by stages to 1.05 gr. Total dose given 6.4 gr. At the third injection jaundice improved, and continued to do so. The W.R. at the end of six weeks was negative, which it has remained for seven years without further treatment.

(3) Case reported by Milian. A secondary syphilitic, W.R. ++. Had a rash diagnosed as a biotropic phenomenon, i.e., Milian's erythema of the ninth day. Treatment was suspended for sixteen days, when she developed an intense jaundice. There was, however, no fever and no digestive disorder. In view of the difficulty of being certain that the jaundice was not toxic, treatment was continued by mercury cyanide. At this moment she developed a severe frontal headache, and the Wasserman which after two injections had become +, became ++ again. N.A.B. was again given, only in a higher dose, 0.6 instead of 0.45, and from that moment the patient never looked back, all grave symptoms vanishing in thirty-six hours.

These cases are certainly striking. No cases at all comparable were found in the St. George's series. The possible explanation may be that the patients were never treated by arsenic alone.

Two of the cases would uphold Milian's contention, that arsenic in small doses followed by an interval, is apt to be dangerous. The same cannot be said of the first case, when an enormous dose was given in a very short time. Yet this case, in addition to the other two, was certainly not toxic, for more and higher doses did not aggravate the jaundice but apparently cured it. At any rate, the jaundice which had been getting worse, rapidly improved together with the signs of syphilitic activity.

Out of the St. George's series there were five cases which had only about 1.5 gr. of arsenic and then absented themselves for various reasons, returning with jaundice between two and three months. Their subsequent history in no way differed from the great majority of the others, namely symptomless jaundice which disappeared in due course without any active anti-syphilitic treatment. They had, of course, had a small amount of bismuth together with the arsenic.

In a general criticism of Milian's views, one must at least pay due respect to him for having laid the toxic ghost. His insistence on the preponderant part played by syphilis in the production of jaundice, particularly in post-therapeutic cases, cannot be said to have as yet met with general agreement, particularly in this country. But the fact that
he was able to treat 79 cases out of 102 with further doses of arsenic without making the jaundice worse must, one would think, drive home the lesson that the toxic theory has been in the past overdone.

The St. George's series of post-therapeutic cases are particularly interesting compared with Milian's, as they provide the reverse of the medal. They were all treated as toxic cases, and none of them showed signs of being any the worse for it. Unfortunately, full clinical histories and personal examination was impossible in all the cases. Such records as were available, for most of the patients refused to come to hospital, and such cases as were seen in the recent three years, corresponded more or less accurately to Milian's description of syphilitic jaundice. That is to say, fever was absent, tongue was clean, &c.

Only if the jaundice continued unabated for more than two or three weeks, which was the exception, could the patient be persuaded to come to hospital. When this occurred, the jaundice did gradually recover, but it could not be said that credit could be given to any particular method of treatment. As a general rule, this consisted of diet, cholagogues, and, in recent years, the administration of sodium thiosulphate by daily intravenous injection for eight to ten days.

There was no record of a mucous or a cutaneous relapse in any of the patients.

A particular survey was made of the Wassermann reaction before and after the jaundice.

Primary and Secondary Cases.

The Wassermann was only properly controlled for this purpose in twenty-four cases. In eighteen of these it was negative at the time of the jaundice, and has remained so while the patient has been under observation. This has been for an average period for two years. In only six cases did the W.R. give any indication of syphilitic activity at the time of the jaundice. In detail, these six cases were:

(1) Sero-negative case with jaundice occurring one month after the first course. W.R. at the time of jaundice was not quite negative. After a second course of bismuth it was unaltered; after further bismuth, negative.

This case only shows that there was a relative lack of response to treatment. It is, of course, permissible to speculate that had arsenic been restarted that the W.R. might have become negative sooner.

(2) Sero-positive case with jaundice occurring two months after the first course. W.R. positive at the end of the first course and at the time of jaundice.

This, of course, is no proof as to the syphilitic nature of the jaundice.

(3) Sero-positive case with jaundice occurring two months after the first course. W.R. positive at the time of jaundice, became negative after treatment with bismuth over eight months. Subsequently relapsed positive and remained so for two years.

Here, the W.R. is no proof in favour of the syphilitic nature of the jaundice, but the subsequent history of the syphilis is unsatisfactory. Conceivably, the jaundice played some part in allowing the syphilis to become Wassermann-fast.

(4) Secondary case with jaundice two and a half months after first course. W.R. negative at the end of the first course, but at the time of jaundice positive. It remained positive in spite of treatment with calomel over two years; subsequent history unknown.

This definitely suggests a hepato-recidive with bad results following upon the abstention from arsenic.
(5) Sero-positive case. After two courses the W.R. was negative. After the first N.A.B. of third course, felt ill with pains in the joints and slight jaundice; W.R. +. After two weeks two injections of grey oil, then four of N.A.B., W.R. negative.

This is the only case which in some respects resembles those quoted by Milian, in that arsenic was resumed with good results on the W.R. and no ill-effects on the jaundice.

**Tertiary Cases.**

W.R. was only adequately controlled in thirty-five cases. It was positive at the time of jaundice in twenty-six, nine of whom were subsequently found to be Wassermann-fast. The other seventeen became subsequently negative, although they did not all remain so. In nine cases the W.R. was negative at the time of the jaundice, and has remained so.

It must be admitted that the possibility of error in these results is considerable; the W.R. was not taken automatically at the beginning of jaundice and repeated throughout its course; it was taken as a routine after the first course, and again before the beginning of the next, i.e., at the end of the rest interval and iodides. Since the maximum incidence of the jaundice varied between two and three months after the first course, this coincided with the scheduled time for starting the next course; the W.R. taken, therefore, about that date coincided in many cases with the jaundice.

Other records simply state the W.R. as being negative or positive at the time of jaundice. Thus Sezary, out of twenty-four cases, quotes nine as being positive at the time of jaundice and eleven negative. Filiol simply states 50 per cent. as being negative at the time of jaundice. Milian does not quote the actual blood-findings in the bulk of the cases he regarded as hepato-recidives.

Obviously, however, the mere record of the Wassermann being positive or negative at the time of the jaundice means little unless we know its previous behaviour and subsequent history. The St. George's figures, however, although far from being perfect, do rather suggest that in the vast majority of cases which satisfied Milian's requirements as being hepato-recidives, that the Wassermann had not altered to the positive side. Now it has been held that a hepato-recidive is unlikely to occur in a large and important organ like the liver without influencing the W.R. It is, however, a perfectly possible speculation to indulge in that antecedent treatment with arsenic may mask the W.R., but not prevent a syphilitic relapse. The following case is an example of how early but insufficient treatment may not prevent undoubted syphilitic activity and yet the W.R. be uninfluenced.

The patient, aged 30, was seen with a chancre of one week's duration, whose W.R. was negative. He had three injections of N.A.B. (dose unknown) and bismuth over three weeks. At the third injection he had a nitroidal crisis which alarmed him very much. He absented himself from further treatment. He was again seen at a date which was nine weeks after the first appearance of the chancre, complaining of headaches and general malaise. He had undoubted secondaries in the scalp, together with enlarged glands in the neck and both epitrochlears. The W.R. was completely negative. Treatment was again instituted in the form of sulphostab and bismuth, which caused a rapid disappearance of the secondary lesions. During the course of the next six months, his W.R. was on one occasion found to be just positive. This type of case is probably far from rare.
French opinion in general appears to accept Milian's view in so far as admitting that a certain number of cases are hepato-recidives when occurring post-therapeutically, or may be due to a relative arsenic resistance when occurring intra-therapeutically. But in view of the great difficulty of being absolutely certain as to the correct ætiology, they do not advise the continuation of arsenic. Ravaut reports the following case:—

Secondary syphilitic treated with eight injections of N.A.B., highest dose 0'75, together with eight injections of mercury. Two months later she returned with jaundice, and was treated for eight days with calomel by the mouth. Jaundice progressed. Arsenic was therefore restarted in doses of 0'15 and 0'3. Several days afterwards there appeared multiple hæmorrhages, in spite of which two more injections of N.A.B. were given, and the patient died in coma almost at once. Hence Ravaut recommends that even in cases which are suspected as being hepato-recidives, or due to the syphilis in any way, that treatment should only be continued by means of bismuth, and not by arsenic for fear of lighting on a toxic case. (This is obviously the procedure which is likely to appeal to most people, for even if one does not agree that the jaundice is syphilitic in any way, yet there are very distinct disadvantages in allowing it to interrupt the normal rhythm of the anti-syphilitic treatment, particularly as jaundice has been found to be particularly likely to occur during the first six months of treatment, when it is usually agreed that therapy must be at its most active.)

Milian's original contention, however, obtains support from Greenbaum [6], who reports the following very interesting case:—

A patient, a secondary syphilitic with a roseolar rash, had received four injections of N.A.B., totalling 1'5 gr. She then absented herself from treatment for three and a half months, after which time she returned with jaundice. On examination there were still remains of the original secondary rash, together with an ulcerating lesion of the vagina, which was regarded as syphilitic. The liver on examination was smaller than normal; the W.R. is not recorded.

Greenbaum regarded her as being a hepato-recidive, and she was given potassium bismuth tartrate 100 mg. Two days later, however, she returned, with the jaundice much worse, and was admitted into hospital. A petechial rash developed and coma ensued, death occurring one week after her reappearance. Post-mortem: The liver was small, weighing 510 gr.; pale brownish in colour. The cut surface showed irregular light areas which formed a contrast to the brown of the rest of the tissue. Histology: Post-mortem changes were extensive. No normal liver cells were to be seen, many having completely disappeared; others were ragged, granular, anuclear masses of protoplasm. Between the nodules there was considerable infiltration of lymphocytes and mononuclear wandering cells. The post-mortem diagnosis was, therefore, regarded to be toxic hepatitis of the nature of acute yellow atrophy.

In his criticism of the case, Greenbaum quotes Milian's views with commendation. He much regretted that he did not at once put this patient on arsenic in big doses, which might have had a chance of acting in time to arrest the syphilitic process. For such he firmly regarded it as being, namely, a hepato-recidive of the liver, which had developed into atrophy caused by the syphilis and not by the arsenic, for, in his words: "No known drug in tolerated doses in such small amounts will produce poisoning almost four months after injection." He concludes: "While it is true that it is best to avoid treating with arsenic icterus occurring during the course of treatment, certainly it
seems as if the pendulum has swung too far the other way, and that at least the post-
therapeutic type of icterus should not be included in their entirety in this category."

If one agrees with Greenbaum that an arsenical intoxication is out of the question
after three and a half months, then one must agree with him that it is a pity arsenic was
not tried. Marcel Pinard's two cases previously quoted confirm Milian's statement that
increased doses of arsenic have been known to cause quick recovery in a patient with
an apparent commencing liver atrophy. As long as one can safely assume that there is
no arseno-toxic element present, then arsenic may do good, and it is doubtful whether it
would do harm to an acute atrophy of an idiopathic nature. His view as to the
impossibility of an arseno-toxic aetiology based upon the three a half months interval
is, of course, open to question. The toxic school usually points out that cases of
liver atrophy occurred in T.N.T. and trichlorethylene poisoning in some instances some
time after the patients had ceased working with these compounds. Panton, in discussing
them, mentions that some weeks sometimes elapsed before the acute liver symptoms arose,
during which time they had not been in contact with the drug. There were, however,
usually premonitory symptoms whilst they were at work. I have not been able to find
any definite statement as to the longest time interval recorded before the onset of
atrophy in these cases. There is, however, a big difference between saturation in the
atmosphere of the drug and the administration of such a few doses as occurred in
Greenbaum's case.

There remain two other theories to be examined briefly before attempting to arrive
at any conclusions. One is the catarrhal theory, and the other what Ravaut terms the
"confit therapeutique."

**Catarrhal Theory.**

Ruge, in his survey, expressed his regret that he was unable, in spite of his huge
figures, to arrive at any definite conclusions as to the aetiology of N.A.B. jaundice, but
points out that, in his opinion, it is identical in nature with that of catarrhal jaundice.

His reasons for doing so are cogent enough. He found that charted over years the
curve of the incidence of the N.A.B. jaundice kept remarkably parallel with that of
catarrhal jaundice. As his figures are large, 730 cases of N.A.B. jaundice and 1,723
cases of catarrhal jaundice, this finding must command our respect. Further, he finds
that the other theories of the possible causation of N.A.B. jaundice are quite inadequate
to account for the very considerable increase in such jaundice which has taken place in
the ten years 1919-29 as compared with the ten years 1909-19.

Ruge stated that his N.A.B. jaundice was particularly likely to occur after the first
course of arsenic, the greatest incidence being after six to eight weeks. This he attempts
to explain as due to the sensitization of the liver by the arsenic to the infecting organism
(unknown). During later courses of arsenic he supposes that the liver has acquired
immunity from the drug.

It will be seen that this point of view is very similar with Milian's theory of bio-
tropism, only that Ruge suggests that the liver is made more sensitive to the infecting
organisms, while for Milian the infecting organisms are stirred up into activity by the action
of the N.A.B. Milian, however, only considers that this is likely to occur in the intra-
therapeutic cases, while for Ruge this sensitization takes six to eight weeks before it
develops into a full-blown jaundice. It may well be that catarrhal jaundice has an
incubation period of some three months, but on the whole I must say that Milian's
suggestion seems the more likely.
Ruge points out what many of the French authors emphasize, that clinical differences between catarrhal jaundice and N.A.B. jaundice hardly exist. In this connection, a paper by Lerman [7] may be mentioned. This author compared the clinical picture in detail of a group of arsenical jaundice and a group of catarrhal. His findings were:

That the symptoms of arsenical jaundice were milder than in catarrhal jaundice; pyrexia and prostration were rare, similarly a tender liver and a palpable spleen, whilst in catarrhal jaundice a tender liver was fairly common and, less frequently, a palpable spleen.

He found slight differences in the blood picture. In arsenical jaundice slight leucocytosis and a normal differential count, in catarrhal jaundice the characteristic leucopenia with relative lymphocytosis.

Ruge stated that his N.A.B. jaundice on the whole ran a severer course than the catarrhal group; his death rate was higher. In the simple jaundice group there were two deaths, i.e., 1 per cent. One was an acute atrophy, and the other cirrhosis. In the N.A.B. group there were eight deaths, 12 per cent. These all died of acute atrophy. Two of these he regarded as toxic, in that there was a concurrent dermatitis. The others he regarded as idiopathic acute yellow atrophy.

Stokes [8] is also of the opinion that an infectious agent is the cause of a large number of cases of jaundice following treatment. In his words: "Infectious epidemic catarrhal jaundice in our experience is the commonest hepatic disturbance encountered in treating syphilis at the present day." It must also be said that Stokes pays due deference to the existence of hepato-recidives, which, as he points out, is likely to be a manifestation occurring in the intervals of treatment.

Conflit Therapeutique.

This theory merely states that the jaundice is caused by the factor arsenic plus the factor syphilis. It is, in fact, a species of Herxheimer reaction due to the toxins liberated by the spirochaetes under the influence of treatment. Filiol claims that it satisfactorily explains all the known facts, i.e., that jaundice is commonest at the beginning of treatment when both the syphilis and the treatment are at their most intense, and also that it can appear after the course of treatment when all the other signs of syphilis are in regression. He agrees that the jaundice clinically most frequently takes the form of simple catarrhal jaundice.

Such, then, are the current theories by which we have to try and assess the cause of arsenical jaundice.

Firstly, one must remember that jaundice is only a liver symptom, and that any of the usual medical or surgical conditions which give rise to it may be present in a syphilitic undergoing treatment as in any other section of the community. The toxic phobia is rather apt to blind one to this fact. For instance, one of our cases developed jaundice after the usual two and a half months interval. He made a partial recovery as an outpatient, but one month later was admitted into another hospital and operated on for gall stones, which were numerous.

In the main, however, the striking periodicity with which jaundice has supervened in the St. George's cases after the first course and with an interval reaching a sharp peak between two and three months suggests, one would think, that there is an uniform cause in the bulk of the cases. None of the current theories seem to explain these post-therapeutic cases of our series very satisfactorily.
It is impossible to deny that they may possibly be all due to a mild intercurrent infection such as catarrhal jaundice, and that their intimate connection with the first course may be due to a biotrophic action of the arsenic, or the infecting organism, or a debilitary effect of the arsenic on the liver. But it is difficult to see why this should reach a sharp peak amounting to nearly 50 per cent of all cases after an interval of two to three months.

Milian would certainly say that they were all hepato-recidives, and, what is more, caused by an insufficient amount of arsenic followed by too long a rest interval. Now, again it is perfectly possible that these two last factors may have played a very considerable part in the production of the jaundice, but such evidence as is available does not suggest that the jaundice can be regarded as syphilitic, judging it from the Wassermann reaction, absence of other syphilitic symptoms, and the subsequently favourable outcome of further anti-syphilitic treatment, even though carried on solely by bismuth or mercury. For, on the whole, with the few exceptions which have been mentioned, the syphilis of the patients who had had jaundice seemed to run a particularly benign course. As one patient expressed himself, “The jaundice seemed to get the trouble out of the system.” Whether this impression has any reality requires an examination of the subsequent histories of a large number of cases over a number of years.

Milian’s experiences, however, with similar post-therapeutic cases render it extremely unlikely that more than a very small percentage of them are toxic in any way.

Turning to the “Conflit thérapeutique” theory, one must allow that the factor arsenic plus syphilis certainly seems to be indispensable in the majority of the cases; but, again, it is difficult to see why the toxins liberated by their conjugation should take two to three months before they cause jaundice. The simple Herxheimer reaction, when it takes place on the skin, usually occurs fairly soon after an injection of arsenic.

While, then, this theory appears to offer the most probable explanation in principle, yet the supposed mechanism by which it acts appears unsatisfactory. Unfortunately, the question is of more than academic interest. It is true it does not seem to matter very much in the bulk of the cases what view is taken of the aetiology of the jaundice. For instance, Milian’s were all treated with further arsenic, and in ours, arsenic was withheld for eighteen months, yet the results appear to be identical, both with regard to the immediate outcome of their jaundice and their syphilis. Yet fatal cases are comparatively common, some of which appear to be undoubtedly toxic in that there was a concurrent dermatitis; others are assumed to be idiopathic yellow atrophy of an infective nature, and others appear to be definitely syphilitic.

In the St. George’s series there were two fatal cases, i.e., about 2 per cent., which compares with Ruge’s percentage of 1·7 per cent.

(1) A man of 47 diagnosed as congenital. Treated twelve years previously with twelve injections of “606” and eight of mercury. Wassermann persistently positive. He came under observation suffering from double primary optic atrophy. After the first injection of N.A.B., he complained of pains all over. There is no record of any further reaction until the fifth injection, when he complained of giddiness and pains in the leg and vomiting. Jaundice ensued after fourteen days interval. The next day he was admitted to hospital with deep jaundice, temperature 104°F., pulse 120. Coma rapidly set in, and death occurred in five days.

At the post-mortem, all the organs were congested, numerous petechiae in the skin,
myocardium and pericardium. The liver weighed 54 oz., was pale yellow in colour, very soft in consistency, and the outlines of the lobes not distinct.


In both our cases, as in most of the published fatal cases, the total amount of arsenic given has been very small, which gives some credence to the theory that the toxic factor is not the only one in producing the fatal termination. In one of our cases there was certainly a concurrent dermatitis. This notoriously occurs frequently enough after very small doses of arsenic, and presumably the same factor which produces the dermatitis, be it toxic or in the nature of a sensitization, will also affect the liver.

Our other case, it will be noticed, had previously received twelve injections of "606" some twelve years before coming under observation. This should have disposed of any sensitizing effect; also, "606" is much more toxic than N.A.B. In his case, therefore, the part played by the subsequent arsenic he received is much more equivocal. It would be as easy to explain his fatal hepatitis, for the post-mortem findings were by no means typical of acute yellow atrophy, by the progressive action of the syphilis on his liver for the twelve years with which he was without treatment. The final flare up might well have been in the nature of a Herxheimer reaction or a reactivation of the syphilis.

Summing up, therefore, one can say that jaundice occurs most commonly as a result of the interplay of arsenic and syphilis in the liver. Cases which occur during a course, or soon after, are particularly likely to be due to the arsenical factor, either directly as a toxic effect, or from its Herxheimer or biotropic action. In the large bulk of the cases, however, a practically symptomless jaundice is apt to occur some time after the first course, in which the suspicion appears to be justified that the syphilitic factor is more responsible. Yet in the vast majority of the cases the appearance of such post-therapeutic jaundice does not appear to indicate that the syphilis is going to run a particularly resistant or malignant course.

From the practical standpoint of treatment, the position is fairly clear, for whatever is done the jaundice usually gets better. Giving more arsenic is hardly worth it, since the treatment can be carried on by bismuth without the attendant risk of dropping on a masked toxic case. There seems to be no reason why arsenic should not be safely continued with as soon as the jaundice has recovered, unless there have been obvious signs of arsenical intoxication such as a dermatitis, which would preclude it in any case.

With regard to prevention of the occurrence of jaundice, this is going to be somewhat difficult until we know more about its exact aetiology. During the last eight years, 4 oz. of 50 per cent. glucose has been given at St. George's prior to the injection of arsenic, and the usual precautions have been taken with regard to meals. In my opinion, it is doubtful whether this has made any difference. Obviously any of the predisposing causes of catarrhal jaundice or other intercurrent jaundice will act more actively on a person whose liver is already a battle-ground of one of the most formidable contests staged by modern chemotherapy.
As a purely empiric measure, one wonders, when 80 per cent. of the cases appear so monotonously with a definite time relation to the first course, whether anything could be done by reorganizing the first course of treatment, so that the patient could be kept more continuously under arsenic the whole of the first six months of his treatment.

Such a scheme of treatment could easily enough be arranged without increasing the total amount of arsenic, which is very variously considered to be essential, for instance, by heightening the individual dose up to 0.75 or 0.9 gr. and lengthening the interval of injections to two or three weeks.

REFERENCES.


APPENDICOSTOMY.

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In the British Medical Journal of 1894 (Vol. II, p. 1112) there occurs an account of a meeting of the Medical Society of London, at which Mr. Goodsall showed a man who had come into hospital for intestinal obstruction, caused by cancer of the rectum. At operation he found the sigmoid could not be brought up to the surface, and the abdomen was closed, but on account of increasing obstruction he operated again several days later. He cut down upon the cæcum, and after some manipulation he managed to get it to the surface and opened it immediately. The patient was left for two days on the operating table in order to avoid undue risk of peritoneal infection, and he made a good recovery. In the subsequent discussion, Mr. C. B. Keetley "suggested that when it was necessary to empty the cæcum at once, the vermiform appendix might be made use of as a spout."

This appears to be the first recorded suggestion for appendicostomy, and was further elaborated in a valuable paper by Mr. Keetley [1] in 1905. In the interval the operation was actually accomplished and first described in 1902 by Dr. Robert F. Weir [2], of New York, under the following title: "A New Use for the Useless Appendix in the Surgical Treatment of Obstinate Colitis." The following account of his case is taken from Moynihan's "Abdominal Operations," Vol. II.

"A young man, aged 31, had had for nearly three years persistent diarræa, associated lately with the passage of blood. An exploratory incision above the umbilicus showed thickening and congestion of the colon. It was then determined to resort to a cæcal fistula, and the usual incision with intermuscular separation was made. As the cæcum was exposed the appendix rose so suggestively into view, that I determined to