BISMUTH THERAPY IN JAUNDICE DURING ANTISYPHILITIC TREATMENT

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Considerable attention has been paid of late to the problem of hepatic jaundice arising during the course of antisiphilic therapy. For some time it has been the prevalent belief that such "therapy jaundice" is in the main due to toxic liver damage by the metals employed, with a superadded precipitating factor of infective nature. Recent work, however, has cast doubt upon this dual hypothesis, the toxic factor being thrust more and more into the background. Dible and McMichael (1943) have shown that the histological appearances of the hepatic lesions are not like those produced by arsenic poisoning in experimental animals, but are similar to those found in serum jaundice or epidemic hepatitis. They further point out that the incidence and severity of therapy jaundice bear no relation to the total quantity of arsenic or bismuth given. These and other observations appear to minimize, though they cannot be said to eliminate entirely, the toxic factor in the aetiology of such jaundice. The problem still awaits final solution.

Until the question of aetiology is settled, the further question of whether or not to continue antisiphilic therapy during the jaundice cannot be satisfactorily answered. Stokes and Ruedemann (1920) claimed to have continued arsenotherapy in 11 patients "without apparent ill effect." Wile and Sams (1934) reported 5 similar cases in which arsenic was continued; one died, and the other four recovered normally. The commoner and more cautious practice is, however, to discontinue arsenic and to continue with bismuth alone in order to avoid a gap in treatment. But even bismuth is not without toxic potentialities, and it is evident that, although this metal in therapeutic doses may play only a very minor part in producing damage in a normal liver, its action on an already weakened organ might be of considerable importance. One's clinical impression is that bismuth does not appear to cause harm to jaundiced patients. But clinical impressions are not always reliable. An attempt to test the validity of this one is embodied in the investigation described below.

Method

One method of approaching the problem seemed to be to determine whether the continuance of bismuth injections materially delayed recovery of hepatic function in cases of therapy jaundice. Soffer (1937) claimed that it did not, but the figures he quotes to prove his assertion are not sufficiently detailed to allow of statistical analysis, and are therefore valueless. In the present experiment two groups of sufferers were compared. One group received intramuscular injections of 2 c.cm. of bicreol (3 g. of bismuth metal) weekly throughout the illness; the other did not. Arsenotherapy was not given to either group while jaundiced, nor for some time afterwards. Care was taken that in all other respects the groups were strictly comparable. All patients were young (in the third or fourth decade) and otherwise fit Naval or Air Force ratings; they were selected at random from the routine admissions to a Royal Naval hospital in England between Jan. and April, 1944; they were all early syphilitics, though at different stages of treatment; they had all previously received both arsenic and bismuth therapy; and in no case were other aetiological factors for the jaundice present. All patients were kept in bed till their liver function was normal, and received no other form of treatment except a low-fat diet. So far as could be ascertained, no case, after recovery, relapsed during the period over which the experiment was conducted. Four patients had had one previous attack of jaundice during the course of their treatment, but the attack had cleared up at least two months before the onset of the present illness.

The recovery period in each case was recorded. It was assessed as the number of days from the onset of symptoms to complete recovery of normal liver function, as measured by the oral Quick hippuric-acid-excretion test (Kolmer and

Boerner, 1941). "Complete" recovery of function was assumed to have occurred when the test gave excretion values of at least 2.55 g. of benzoic acid (3.75 g. hippuric acid). Such tests were performed bi-weekly, so that the recorded recovery periods are only approximate. This does not matter, however, as in comparing the two groups a difference in mean recovery periods of a day or two would not be clinically significant. One was seeking a difference of a week or more.

(It is of interest to note that in most cases return of the liver function test to normal coincided closely with disappearance of clinical jaundice. In a few cases, however, a trace of icterus lingered in the conjunctivae for two or three days after the test had reached normal.)

Results

Ten patients received bismuth therapy during the course of their illness. Their recovery periods (in days) were: 14, 17, 21, 24, 26, 30, 31, 38, 40, 44 (mean, 28.5 days). Eleven patients received no bismuth during the course of their illness. Their recovery periods (in days) were: 19, 20, 25, 30, 34, 36, 37, 41, 41, 47, 48 (mean, 34.4 days).

The "bismuth" group therefore recovered on the whole slightly more rapidly than the "non-bismuth" group, but the difference between the two means is statistically quite non-significant. However, on the basis of the above experiment, the odds against the hypothesis that the administration of bismuth retards recovery by as much as seven days are about 100 to 1. Thus, owing to the fortunate circumstance that the (non-significant) difference between the groups happens to be in favour of the "bismuth" group, even so small a series as this provides good evidence that any retardation of recovery by bismuth must be very slight, and doubtless for practical purposes negligible.

Comment

It is not, of course, claimed that this experiment is conclusive. One obvious criticism is that a normal Quick test does not necessarily indicate a completely normal liver function. Furthermore, the functional reserves of the liver are great, and a damaged liver may still function apparently quite normally. There is thus no guarantee that the "bismuth" group did not in reality suffer more destruction of liver tissue and more permanent (though undetectable) damage than the "non-bismuth" group. There is, on the other hand, equally no evidence that it did. A study of the relapse rates of two similar groups might prove illuminating, but such an investigation would be fraught (as indeed is the whole subject) with difficulty. Nevertheless, the result of the present experiment does tend to confirm one's clinical impression that the continuation of bismuth injections is not significantly harmful in the presence of jaundice during antisiphilic treatment.

Summary

A study has been made of the recovery of liver function (as judged by the Quick hippuric-acid-excretion test) in two groups of patients suffering from jaundice during antisiphilic therapy. One group was treated throughout the illness with bismuth; the other received no antisiphilic treatment.

The result of the experiment strongly suggests that bismuth does not significantly retard recovery of liver function in such patients.

Such a result supports the view that bismuth therapy should be continued in the presence of jaundice of this nature.

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T. C. Jaiply (*Amer. J. med. Sci.*, 1943, **206**, 453), who reports an illustrative case with a review of the literature, states that aneurysms of the coeliac artery are rare, only 32 cases confirmed by necropsy having been recorded. The present case was that of a negro aged 44: the signs and symptoms were those of acute cholecystitis. The case, which was one of sacular aneurysm, was complicated by bleeding into the intestinal canal by way of the pancreatic duct.