The trouble in assessing these results is the lack of satisfactory control groups, and there is no doubt that in some conditions a certain proportion of these people tend to get well themselves in the course of time. Any satisfactory investigation would require to distinguish not only loss of symptoms but durability of cure and its other features, such as the change in the social qualities of the patient concerned and the improvement in his general adaptation to life. Among cases of the obsessional or obsessive-compulsive variety the data are conflicting; I have no doubt that there are some cases which without special treatment would not improve at all or would improve very little, but it has to be remembered that here also there is a spontaneous recovery rate. I find statistics of this sort very unsatisfactory and the individual case much more convincing. Statistics should also take into account the duration of a treated case compared with one untreated. I believe that with treatment many psychoneurotic illnesses are shortened; and this, in fact, it would be fair to say—that psychoneurotic conditions are among the most curable of the chronic illnesses the doctor is called upon to treat.

Conclusion

There is an outstanding fact which should commend the practice of psychological medicine to the clinician—and the family doctor is first and foremost a clinician. It is this: that psychological medicine remains pre-eminently a field in which the clinical method, independent of the laboratory and the test-tube, is still the fundamental one. Even the most recondite psychiatric history—such as, for example, that which psychoanalysis involves—is essentially a clinical history of the patient. This history of the patient, which should be a history not only of his symptoms but of his life as an individual, is both a means of diagnosis and the foundation of treatment. For diagnosis, of course, one has to know as well the natural history of physical diseases, while to use the detailed history for the purpose of treatment requires a knowledge of the principles of psychological medicine. But these principles in what I have called the “situational,” and even in many of the historically determined conditions, are simple and can be applied successfully by anyone who cares to give his attention consistently to this aspect of his practice.

AN EPISODE OF “HOMOLOGOUS SERUM JAUNDICE”*

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The occurrence of jaundice in man after the administration of human blood products (plasma and serum) is now a well-recognized phenomenon, and a review of this “homologous serum jaundice” was recently published. The jaundice, which is of hepatic origin, is readily distinguished from the haemolytic icterus which may arise immediately after transfusion with incompatible blood or out-of-date stored blood. Clinically it is similar to, if not indistinguishable from, epidemic hepatitis (catarrhal jaundice), but the incubation period is unusually long—commonly from 2 to 3 months, in contradistinction to the 20- to 40-day period believed to occur in epidemic hepatitis.

A high incidence (57%) of this jaundice has been observed among 71 subjects during the course of an investigation into allergic reactions to human serum. All these subjects received pooled human serum from a single batch (No. 034); a few of them received in addition whole blood or serum from other batches. Batch 034 was, however, the only common factor, and was clearly incriminated as being icterogenic. Subsequently, icterogenicity was confirmed by the results of the deliberate

administration of batch 034 to four volunteer cases of rheumatoid arthritis in which it was desired to produce jaundice for therapeutic reasons.

From this experience it is possible to draw certain conclusions concerning the routes of administration and the effective dosage of icterogenic material: some of the findings are therefore reported.

Materials Used

No. 034 was a routine batch of dried serum issued by the Medical Research Council Drying Unit. It had been prepared from 106 litres of pooled, filtered human serum collected in late April, 1943, from donors in the London area. Sterility tests before and after filtration were negative, and the batch was issued in units (bottles) each equivalent to 400 c.cm. of liquid serum. The units were numbered 1 to 250: Nos. 84 to 146 were received by this depot as its quota of the batch and were reserved for purposes of investigation.

The other batches of serum also administered to some of the subjects were:

(a) *Batch 045*.—This was another routine batch of dried human serum issued by the Medical Research Council Drying Unit, and was prepared from 177 litres of serum from donors in the London area and East Sussex. It was collected in early June, 1943, and sterility tests before and after filtration were negative. Nos. 1 to 102 were received at this depot.

(b) *Pool 0*.—This was a small pool of serum prepared locally and, after Seitz filtration, kept frozen until used.

Any bottle of batches 034 and 045 was assumed to be of identical composition with any other bottle in the same batch.

Methods of Administration

Intradermal Tests.—Several bottles of batch 034 dried serum were reconstituted to normal strength with 400 c.cm. of sterile distilled water taken at random from stocks prepared at this depot. The resultant liquid was partitioned in 2-c.cm. aliquots into sterile test-tubes and kept frozen at 5° F. till required. It was used on numerous days, on each of which one or more tubes were thawed out and a sterile tuberculin syringe was charged with the fluid. Any unused fluid remaining in an opened tube was discarded at the end of the day. The same syringe and needle might be employed for several tests on the same day without sterilization between tests, but after each day's use the syringe was cleaned in chromic acid and resterilized. Needles were thoroughly rinsed with water and resterilized daily. Sterilization was by dry heat (160° C. for 2 hours).

For the intradermal test two intracutaneous injections of the reconstituted serum, each of 0.05 c.cm., were made into the skin of the back in parallel with extracts of dust, pollen, animal hair, etc., and carbol saline.

Transfusions.—A bottle of dried serum was reconstituted to 400 c.cm. as above or, in the case of pool 0, the serum was thawed out. Each transfusion was administered in approximately 30 minutes. This applied to all except the four transfusions given to rheumatoid arthritis patients, who each received 50 c.cm. of reconstituted dried serum (batch 034) added to 450 c.cm. of a group O concentrated red cell suspension.

Cases

Group 1.—47 subjects received intradermal skin tests on one to three occasions with batch 034 only. 25 of the 47 were allergic subjects (hay-fever, bronchial asthma, etc.).

Group 2.—9 subjects received intradermal skin tests and serum transfusions on one to three occasions with batch 034 only. 7 of these were allergic subjects.

Group 3.—19 subjects received skin tests or transfusions, or both, with batch 034, and, in addition, tests or transfusions with other human material (pool 0, batch 045, concentrated red cells). Of these, 7 were allergic subjects, 8 were non-allergic controls, and 4 were the cases of rheumatoid arthritis.

Results

All except two subjects who could not be traced were followed up for at least 150 days after exposure. The results

* A report to the Medical Research Council from the S.W. London Blood Supply Depot.

are summarized in the accompanying Table. Of the 47 cases (group 1) who had received batch 034 only as skin tests, 21 developed jaundice. Similarly, of the 9 (group 2) who had batch 034 only as skin tests and transfusions, 5 developed jaundice. The latent period in these cases, calculated from the date of the first or only administration of serum up to the

Table showing Incidence of Jaundice following Intradermal Tests and Transfusions of Reconstituted Dried Serum (Batch 034)

Group	Cases	Clinical Signs		Latent Period	
		Nil	Jaundice	Mean (Days)	Range (Days)
1 Intradermal tests only	47	21	26	71	46-104
2 Intradermal tests and trans- fusions	9	4	5	60	45-79
3 Intradermal tests and/or trans- fusions + other human material	19	8	11	59	45-96

date of onset of the jaundice, was from 45 to 106 days. This is the maximum latent period; it assumes that the patient had been affected by the first introduction of serum. The date of onset of jaundice was taken as the end-point of the latent period, since in most cases, in retrospect, it was possible to ascertain this date, whereas the date of onset of prodromal symptoms could not be determined.

Of the 19 cases (group 3) who received other materials as well as batch 034, 11 developed jaundice. The latent period, calculated from the date of the first or only administration of batch 034, ranged from 45 to 96 days. Several subjects in this group received material from batch 045. From subsequent investigations there is reason to believe that this batch is also icterogenic.

The attack rate was of the same order whether the serum had been given intradermally or intravenously, and whether it had been given as a single dose or in repeated doses. The severity of hepatitis, which in all cases was mild or moderate in degree only, also appeared to be unrelated to the size, the route, or the frequency of injection. There was a suggestion, however, that the latent period was shorter when the material was given in the larger or in repeated doses (see Fig.). There is no evidence, so far, that permanent liver damage ensued.

GROUP	QUANTITY c.cm.	LATENT PERIOD							
I INTRADERMAL TESTS	0.1-0.3	.	.		..	..	..	..	..
II TRANSFUSIONS	1200 800	.	.	.	.	.	.	.	.
III INTRADERMAL TESTS	0.1-0.3	.	.	.	.	.	.	.	.
TRANSFUSIONS	50-1200	.	..	.	.	.	.	.	.
	DAYS	40	50	60	70	80	90	100	

Chart showing latent periods before onset of jaundice after intradermal tests and transfusions of reconstituted dried serum (batch 034).

The incidence of jaundice was no greater in the allergic subjects than in the normal controls.

Discussion

Since the publication of the Ministry of Health's Memorandum on Homologous Serum Jaundice (1943) the occurrence of the syndrome in this country has been mentioned in several reports (Morgan and Williamson, 1943; Dible, McMichael, and Sherlock, 1943; Steiner, 1944; MacCallum and Bauer, 1944; Beeson, Chesney, and McFarlan, 1944). Nevertheless, the cases of jaundice in the present series had been regarded as "catarrhal jaundice" and the association with the administration of blood products was at first not recognized. The diagnosis of homologous serum jaundice was established only by this follow-up.

When the syndrome occurs after inoculation (measles convalescent serum, yellow-fever vaccine, etc.) it is relatively easy

to detect icterogenic batches of material, because in most instances serum from only a single batch has been given. When jaundice follows transfusion it may be impossible to decide which is the causative batch, because in the usual transfusion practice several batches of plasma or serum may be administered to a single patient and not infrequently whole blood is given as well. In the present series groups 1 and 2 resemble jaundice following inoculation in that only one batch (034) was administered; group 3 cases are more comparable with those seen in transfusion practice, and if groups 1 and 2 had not been studied simultaneously it would have been more difficult to attribute the jaundice to the causative batch. All the subjects, except the 4 cases of rheumatoid arthritis, also received injections of allergens, but we have no reason to believe that these produce hepatitis.

The attack rate—57% of exposed subjects—is the highest so far recorded in any series of homologous serum jaundice. It must, however, be remembered that opportunities for following up in this series were unusually good. The jaundice was not severe and there was apparently no correlation between dosage and virulence. In group 1 the dose was minute (0.1 to 0.3 c.cm.); in group 2 two subjects received 1,200 c.cm. and three subjects 800 c.cm.—that is, 12,000 and 8,000 times the lowest group 1 dose. The group 1 dose is comparable to the dose recorded by MacCallum and Bauer in yellow-fever vaccine jaundice. Intradermal injections would therefore seem to be as effective as the intravenous and subcutaneous routes.

One possible contact case occurred. A subject in group 2, first injected on July 1, 1943, developed jaundice on Aug. 16. A cousin who had been living with this patient until Aug. 9 developed jaundice 31 days after the last contact. This may have been a random case of epidemic hepatitis, but an alternative source of infection could not be established.

In this series the clinical features (Livingstone, personal communication) and the biochemical findings (Gray, personal communication) were indistinguishable from those of epidemic hepatitis. Dible, McMichael, and Sherlock have reported their inability to distinguish histologically between biopsy material from cases of epidemic hepatitis and that from cases of homologous serum jaundice. For the diagnosis of the latter condition, therefore, one must rely upon the history of injection or transfusion of human material during the preceding few months.

Icterogenic batches of human serum and plasma cannot be detected by any laboratory or animal tests. Their recognition is possible only when accurate records of the batch and bottle numbers of blood products given to patients are kept and when a careful follow-up of all recipients is practised for some months afterwards. In the present series the generous co-operation of numerous medical officers of health and practising physicians made a 97% follow-up possible.

Summary

Homologous serum jaundice has followed the administration of a particular batch of pooled human serum.

Jaundice occurred in 57% of the cases exposed.

The dose of homologous serum administered varied from 0.1 to 1,200 c.cm.

The severity of the disease was not related to the dosage of serum given or to the route of administration.

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The Colonial Office has issued through H.M. Stationery Office (Colonial No. 187; price 6d.) a report of the West Indian Conference held in Barbados last March. Among the matters reported on by committees were the means for raising the nutritional level; planning of public works for the improvement of agriculture, education, housing, and public health; and health protection and quarantine. The conference took place under the auspices of the Anglo-American Caribbean Commission, and it is planned to hold another within the next ten months.