Section of Epidemiology and State Medicine

President—P. G. Stock, C.B., C.B.E., F.R.C.P., D.P.H.

[*March* 22, 1946]

Meeting Held at the Medical Society of London, 11, Chandos Street, London, W.1.

Homologous Serum Jaundice

By W. H. Bradley, D.M.

Senior Medical Officer, Ministry of Health

In May 1937 the two children of a well-to-do family living near Oxford died on consecutive days of acute yellow atrophy of the liver. Four days before death one child, a girl aged 7, vomited after breakfast but was able to travel with her mother to London and back by train. She vomited again after returning home, and was restless during the night. On the second day she was at first sleepy but later irritable: the restlessness became marked and she complained of some abdominal pain. Her doctor, a careful man, found no signs of physical disease and the mother chastised the child for screaming and behaving irrationally. Next day the condition changed dramatically, the child vomited altered blood, became uncontrollable and for the first time was noticed to be slightly jaundiced. She died twenty-four hours later after a period of coma with marked neurological signs.

The 4½-year-old brother's illness began a day after his sister's and ran an almost identical course. Their nurse also developed jaundice but survived.

Measles serum jaundice.—During an inquiry by Medical Officers to the Ministry of Health, it became known that, within a month, two other young children in Oxford had died of hepatic necrosis after similar illnesses and that all four and the nurse had received injections of a single batch of measles convalescent serum nine or ten weeks previously. Eventually 109 recipients of this batch of serum were traced; 41 scattered over nine widely separated areas in England subsequently became ill, 37 of them with jaundice, and 8 died of hepatic necrosis: a phenomenally high fatality rate of 12%. More significantly they all died between the 61st and 93rd day after receiving serum (MacNalty, 1937; Propert, 1938). Subsequently, and particularly as the result of inquiries made by the Medical Officer of Health for Leeds (Jervis, 1940), a few other batches of

measles serum were suspected of being icterogenic, one with fatal results, but the overall incidence amongst the thousands of persons who had received measles serum was so low that nothing was done to discourage its use. Nevertheless, the distributors of the implicated batches discontinued the preparation.

Yellow fever vaccine jaundice.—A similar sequence of events, following the administration of yellow fever vaccine, was reported by Findlay and MacCallum (1937, 1938) who, in the course of five years, had vaccinated 3,100 persons, 89 of whom developed jaundice two to seven months later. Findlay, MacCallum and Murgatroyd (1939) were satisfied that this hepatitis was not due to the yellow fever virus itself but suspected contamination with an icterogenic agent during tissue culture involving the use of human serum. They changed the strain of seed virus and observed no further cases of jaundice following the next 8,000 vaccinations (Findlay, 1940).

Jaundice with mad staggers in horses.—Both clinically and circumstantially there appeared to be a close analogy between these incidents and jaundice with mad staggers which had, on four occasions, been reported in large herds of horses during the course of immunization with various antigens administered in horse serum (Theiler, 1919; Gordon, 1935; Marsh, 1937; Stagsvold, 1938) and because of this similarity the condition was called *homologous serum jaundice,* a hepatitis characterized by a long incubation period of from two to four months following the administration of blood from the same species. Extensive investigations (1943, Medical Officers to Ministry of Health) were inconclusive but the records of these investigations were to prove of considerable value when, in May 1942, hundreds of U.S. soldiers in transit by ship to the British Isles became jaundiced and the question arose whether they were suffering from a communicable disease and whether the convoys affected should be quarantined.

"Post-vaccinal jaundice."[1]—It was known that during mobilization of the American Army, after the Japanese raid on Pearl Harbour on December 7, 1941, all troops received injections of yellow fever vaccine containing human serum, and in England the tentative conclusion that the men with icterus were suffering from homologous serum jaundice was reached without difficulty. Previous experience had suggested that the condition was rarely, if ever, communicable by natural routes and troop movements were allowed to proceed without restriction. These conclusions were speedily confirmed as the result of the surveys by Colonel J. E. Gordon (U.S.M.C.) in North Ireland which showed that icterogenicity was confined to certain batches of vaccine with adjacent serial numbers, strong evidence that the factor common in the implicated batches was not the tissue culture but the human serum used as a vehicle for the vaccine.

Meanwhile, in America, where the outbreak of yellow fever vaccine jaundice was first noticed in March 1942, Dr. Sawyer's team (1944) immediately began investigations amongst the U.S. troops in California, Hawaiian Islands and Oregon. The team had information concerning an earlier outbreak of yellow fever vaccine jaundice in Brazil (Fox *et al.,* 1942) where the evidence against serum used in the preparation of the vaccine was not at all convincing. However, Sawyer's studies conclusively exonerated the yellow fever virus itself for the same seed contributed to all the American vaccine while icterogenicity appeared to be associated with a few only of the lots used. In fact 9 of 117 lots investigated were responsible for 23,664 cases, an overall incidence of 56·64 per thousand doses of vaccine. On the other hand, 70 lots representing 54·4% of the entire amount of vaccine supplied to the U.S. Army during the period were associated with a jaundice attack rate of only 0·41 per 1,000 doses, a figure falling within the normal expectations of jaundice from natural causes. By chance the U.S. Navy escaped with 691 cases of jaundice associated with 1,645,740 doses of vaccine: an incidence of 1·4 per 1,000; again within normal expectation of jaundice from natural causes. The vaccine supplied to both Army and Navy came from the same source and this strange discrimination was, at first, puzzling, until it was discovered that the Navy had been supplied with a small part of one highly icterogenic batch only. With this batch 271 persons were injected and 31 developed jaundice.

This, the luck of the U.S. Navy, should be remembered for it is typical of the vagaries of incidence, resulting from accidents of distribution, which have added to the difficulties of investigating homologous serum jaundice. In consequence most of the illuminating experiences have arisen fortuitously and not as the result of organized study. One such experience played a considerable part at the time the problem of yellow fever vaccine jaundice arose in American troops approaching the British Isles.

[1] "Post vaccinal jaundice" is the term employed in American literature when referring to yellow fever vaccine jaundice."

Mumps serum jaundice.—The American Red Cross,—Harvard Field Unit at Salisbury, attempted serum prophylaxis against a mumps outbreak in a unit of the British Tank Corps stationed in Dorset. Two batches of pooled serum each from 11 volunteers recently convalescent from mumps were given to 266 and subsequently to 204 of the same men at 14-day intervals. 226 men were followed up. 44·7% developed hepatitis, 44 to 123 days later (Beeson *et al.*, 1944).

Pappataci vaccine jaundice.—A similar experience occurred in Southern Russia in 1939 but did not come to notice in England until after the events already described. In 1937 Sergiev *et al.* (1940) gave injections of active pappataci virus and convalescent serum to 500 persons in a sandfly-fever area on the Black Sea coast. These injections were innocuous. In 1939 a similar trial was made using 0·01 ml. of serum containing virus suspended in unstated quantities of serum from sandfly-fever convalescents. 92 of 350 persons who received this treatment developed jaundice within five months, the majority between the 85th and 95th day after injection. In this instance some of the pappataci virus-containing serum obtained from a patient at the onset of sandfly fever was tested by deliberate injection into four persons, one of whom developed jaundice four months later. If this single experimental case can be taken as proving that the "virus serum" was icterogenic then the main outbreak had resulted from injections of no more than 0·01 ml. of serum.

Post-transfusion hepatitis.—When these several instances (measles and mumps convalescent serum, yellow fever and pappataci vaccines) were considered together it became abundantly clear that human serum had been the vehicle of hepatotoxic agents and at the Ministry of Health it seemed inevitable that transfusions of whole blood or serum would, sooner or later, be found to result in homologous serum jaundice. However, one suggestive case only had come to the Ministry's notice: in 1941, a man with a perforated duodenal ulcer received seven bottles of whole blood and one of plasma in July at Chelmsford and developed profound cholæmia seven weeks later at Wolverhampton; but on the strength of this case a meeting of Civilian and Military Transfusion Officers and other interested persons was called at the Ministry on August 13, 1942. By a surprising coincidence the first intimation of any appreciable trouble following transfusion had been received by one of the Transfusion Officers on the preceding day. This occurred in a group of 50 patients given massive transfusions of serum and plasma by way of treatment for peripheral vascular disease. During these investigations, Morgan and Williamson (1943) traced 15 of these patients and found that 9 had become jaundiced from 49 to 107 days after the last transfusion. In five the illness was severe and protracted.

During 1943 several other observers reported cases of jaundice during the second, third and fourth months after transfusion. Some of these cases died of hepatic necrosis and in view of the comparative rarity of acute yellow atrophy of the liver, even at a time when epidemic hepatitis was prevalent, these few deaths in persons previously transfused were thought to have a significance but it was impossible to *prove* any direct association with the preceding transfusion. However, autopsy and biopsy material from some of these cases was compared with that from measles serum, mumps serum and yellow fever vaccine jaundice, and with N.A.B. jaundice and epidemic hepatitis, by Dible, McMichael *et al.* (1943), who concluded: "Although there may be different ætiological factors in each of the above groups, we have not found any recognizable histological criteria for their differentiation." Differentiation by other laboratory methods proved equally unhelpful and the identification, for the purposes of study, of cases of post-transfusion jaundice had to depend upon the weight of circumstances or some unusual chance such as that which brought "Batch 034" to notice (Bradley, Loutit, Maunsell (1944)). This batch of dried transfusion serum was prepared specially by the M.R.C. Transfusion Reaction Sub-Committee for the purpose of observing the immediate reactions of allergic and normal subjects to skin test doses and subsequent transfusion. Fortunately, some of the recipients remained for several weeks under observation for their allergic condition and were noticed to become jaundiced at about the same time. Follow-up showed that 57% of 75 recipients became jaundiced 45 to 104 days after injection. The incidence of jaundice was no greater in the allergic than in the normal controls. The dose had varied from 0·1 ml. intracutaneously to as much as 1,200 ml. intravenously but there appeared to be no correlation between dosage or route and virulence or icterogenicity.

The hepatitis produced by batch 034 was uniformly mild, a feature which encouraged MacCallum and Bradley (1944) to use it deliberately in the induction of jaundice in intractable cases of rheumatoid arthritis. Our intentions were benign and our objectives two in number: first, to learn something about hepatitis and, secondly, to see whether

Hench's (1938) claim that spontaneous jaundice gave rheumatoids a holiday from their pain was true. While I have little doubt that hepatitis, in some way, interrupts the course of rheumatoid arthritis, I feel strongly that until we understand homologous serum jaundice better it can be used as a therapeutic agent only for research purposes. However, by these experiments on rheumatoids it was proved beyond doubt that the icterogenic agent was resident in the serum and that yellow fever vaccine jaundice and batch 034 jaundice had not resulted from a natural spread of disease or from accidental syringe transmission. For by now we were beginning to suspect that outbreaks of jaundice in arsphenamine, chrysotherapy and other clinics were merely examples of homologous serum jaundice, the icterogenic agent being communicated through imperfectly sterilized syringes (Min. Health, 1945).

The relative benignity of batch 034 and the regularity with which, even after two years of storage, it continued to produce jaundice in about 50% of the volunteers to which it was administered in subsequent trials, were in marked contrast to the virulence and inconsistency of another batch—045—which came under special observation. This batch was brought into use in the "allergic" trials when batch 034 was withdrawn because it had produced jaundice. It first had appeared to be innocuous until two women who had received it and other blood products intravenously died of acute yellow atrophy 97 and 105 days after transfusion. As far as could be ascertained jaundice did not occur in any other recipients of this batch of serum.

By now the Medical Research Council Transfusion Committee had begun to take part in the investigations and the transfusion officers to work out and apply measures calculated to give some control. I will not discuss these measures, which are not particularly hopeful, but will try to give you some idea of the magnitude of the problem.

The E.M.S. statistical office has searched the records of every fifth admission to E.M.S. hospitals for mention of jaundice and transfusion with the following provisional results which have been provided by Dr. Percy Stocks and Miss E. M. Brooke.

JAUNDICE INCIDENCE AFTER BLOOD TRANSFUSION.

Provisional figures obtained up to February 28, 1946, in the course of a search by the Ministry of Health's Statistical Branch at Norcross of E.M.S. Hospital records of 1940-1945 in-patients.

Group whose hospital records were examined	Total patients whose records have been examined to date	Number in whom jaundice developed during observation	Number of those who died subsequently to jaundice	Incidence rate in observation period (and standard error)
Service patients under observation 3 months or more after transfusion or injury (or who developed jaundice within that period)—				
(*a*) Injured patients who were transfused ...	1,316	124	17	94± 8
(*b*) Sick patients who were transfused ...	82	16	7	(195)
(*c*) Injured patients who were not transfused	6,350	6	0	·9±·3
All males in Services aged under 35 in the United Kingdom in 1942-43	About 63,000 coded for all diseases and injuries	About 1,050 admitted with jaundice and no history of transfusion	Not ascertained	About 2 per 1,000 in 3 months

Analysis of jaundice cases in groups (*a*) and (*c*) of above table, according to theatre of war in which injury occurred.

	(*a*) Transfused			(*b*) Not transfused		
Theatre of war	Total examined	Jaundice developed	Died after jaundice	Total examined	Jaundice developed	Died after jaundice
Mediterranean	308	55	6	905	0	0
Western Europe	613	55	9	2,133	0	0
Far East	30	5	1	80	0	0
United Kingdom	107	8	1	1,240	3	0
Not stated	258	1	0	1,992	3	0
Total	1,316	124	17	6,350	6	0

These figures require correction because other causes may have produced jaundice. I have, therefore, scrutinized the histories of 140 cases of jaundice in transfused persons and believe that homologous serum jaundice was the most probable diagnosis in 82 per 1,000 transfused persons with a case fatality of 12%. There is, undoubtedly, a *tertium quid* somewhere in this high fatality and obviously it cannot be concluded that transfusion

fluid was necessarily the vehicle since some of the patients received in addition to transfusion, other parenteral therapies, for example intravenous anæsthetics or penicillin. Unless the hospital records have been grossly misleading it would appear that whole blood has been responsible for hepatitis more frequently than was at first expected. 115 histories state the nature of the blood product transfused. 24 patients received whole blood only, 20 serum or plasma only, and the remaining 71 both whole blood and a product. The experience of the Emergency Medical Service is not unique for at one time in 1945 acute massive necrosis of the liver following transfusion was the major cause of death in U.S. hospitals in the United Kingdom, accidents and pneumonia excepted.

Histology.—I was able to see the case histories and sections from 21 American soldiers dead from this cause. Coma preceded death in all cases; encephalitis was diagnosed in some and jaundice was first noticed after death in 2. The wounds for which the men were transfused were severe in half the cases only, and the patient's condition at the time of onset of hepatitis was fair or good in the majority. The histological appearances suggested that the hepatic necrosis in these fatal cases was sudden and complete and probably preceded or coincided with the onset of symptoms. The biliary passages were patent and healthy, but, unfortunately, there was no statement concerning the presence of bile in the alimentary tract. The livers of those who died before, or within a day or two, of the appearance of jaundice were virtually destroyed, yet showed minimal cellular reaction and no signs of regeneration. Phagocytic infiltration and regeneration of liver columns became more apparent as the interval between jaundice and death increased.

Treatment.—This observation, which is in line with chemical findings, has, I believe, a bearing on treatment, the rationale of which should be to support all the functions, particularly the protein function of the liver until regeneration is well advanced and to reduce energy consumption to a minimum until a weight gain is well established. Dr. Magee will comment on a hopeful line of treatment which has resulted in the only recoveries from coma I have encountered in my series of post-transfusion hepatitis.

Latent period.—Chart I, which includes under "casual" 12 deaths which have been brought to my notice, not as a result of survey, but casually by a Transfusion Officer and others, shows how characteristic is the long interval of two to four months.

Diagnosis.—When the normal expectation of hepatitis from other causes is considered in relation to the figures given for the incidence of jaundice following transfusion (*see*

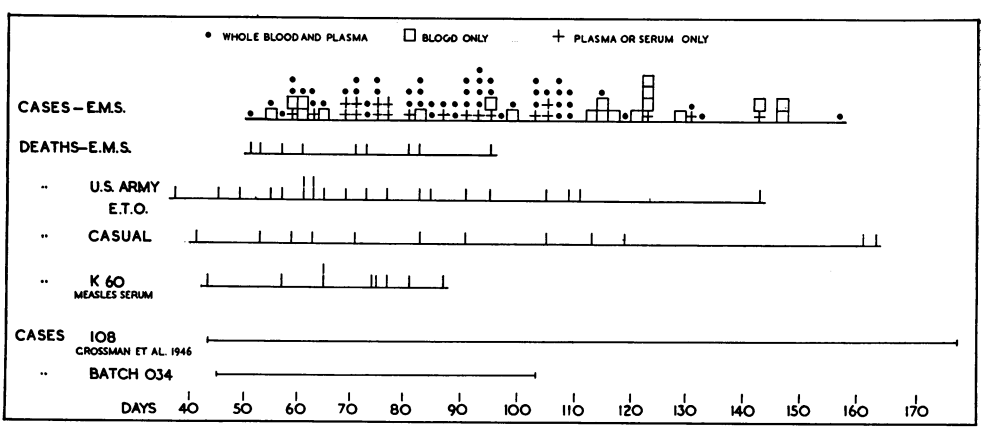
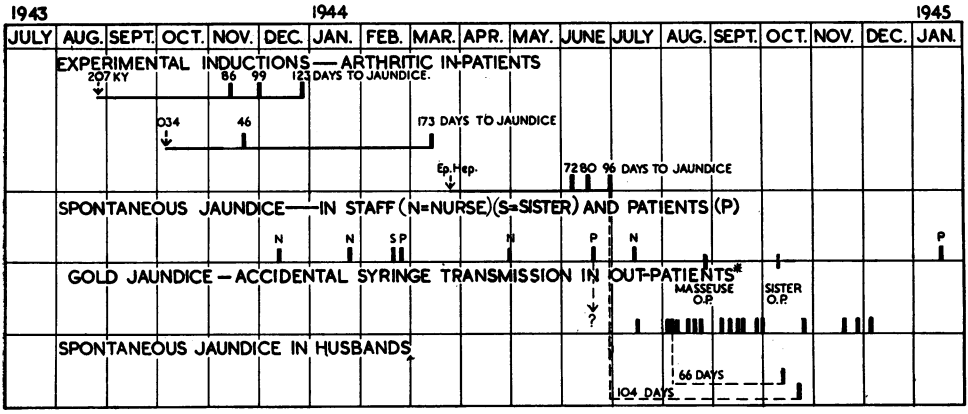


CHART I.—Duration of latent period (days) from transfusion to jaundice.

Table) the following statement appears to be justified: "When hepatitis occurs 40 to 120 days after the administration of a human blood product, or other parenteral therapy, it is almost certainly homologous serum jaundice and must be treated as a disease with an appreciable mortality."

Communicability.—MacCallum (1946) in the paper which follows this will deal with experimental transmissions, but the question still remains whether homologous serum jaundice is ever communicated naturally. I believe it is occasionally, and after a long incubation period. In a previous paper (Min. Health, 1945) an outbreak in a "gold"

clinic is described. Chart II shows the chronology of these events, and indicates the occurrence of jaundice in the husbands of two women with jaundice after intervals of 66 and 104 days.



207 KY = 2·0 c.c. subcutaneously of Batch 207 KY serum given to 10 volunteers.
034 = 50 c.c. intravenously of Batch 034 serum given to 4 patients (*vide* Bradley, Loutit and Maunsell, 1944).
EP.Hep. = 1·25 c.c. subcutaneously of serum from case of epidemic hepatitis given to 6 volunteers.
*Not more than 40 individuals at risk.

CHART II.—Dates of onset of jaundice at a rheumatism clinic.

Conclusion

Post-transfusion jaundice has been of considerable importance during the war. It is an unnatural hazard and doubly tragic because of this and the way in which it has so frequently brought the surgeon's efforts to naught. The need for a method of preventing it without withholding transfusion is great. Furthermore, so long as the hazard of homologous serum jaundice exists we shall hesitate to apply extensively serum or immune globulin prophylaxis in measles, mumps, epidemic hepatitis, influenza and other virus diseases which may be amenable to attenuation or prevention by this method.

Lastly, and perhaps most important, this experience with homologous serum jaundice has shown that small quantities of blood, conveyed during therapy from person to person in a variety of ways, can incidentally carry disease. Whereas jaundice is a striking clinical sign and hepatitis easily diagnosed, less spectacular infections might, on occasion, be passed round by the same means without the accidental nature of the transmission being recognized. Parenteral and blood therapies have provided us with great advantages, but we must keep a watch on them in order to detect and eliminate, as soon as possible, any undesirable features tending to vitiate or discredit them.

Bibliography

BEESON, P. B. *et al.* (1944) *Lancet* (i), 814.
BRADLEY, W. H., LOUTIT, I. F., MAUNSELL, K. (1944) *Brit. Med. J.* (ii), 268.
DIBLE, J. A., McMICHAEL, J., SHERLOCK, S. P. V. (1943) *Lancet* (ii), 402.
FINDLAY, G. M. (1940) *J. R. Army med. Corps*, **74**, 72.
——, and MacCALLUM, F. O. (1937) *Trans. R. Soc. trop. Med. Hyg.*, **31**, 297.
—— —— (1938) *Proc. R. Soc. Med.*, **31**, 799.
—— ——, MURGATROYD, F. (1939) *Trans. R. Soc. trop. Med. Hyg.*, **32**, 575.
FOX, J. P. *et al.* (1942) *Amer. J. Hyg.*, **36**, 68-116.
GORDON, W. S. (1935) Quoted: *Proc. R. Soc. Med.*, **31**, 799.
GROSSMAN, E. B., STEWART, S. G., STOKES, J. (1945) *J. Amer. med. Ass.*, **129**, 991.
HENCH, P. (1938) *Brit. Med. J.* (ii), 394.
JERVIS, J. JOHNSON (1940) Report on the Health Sanitary Administration of Leeds for 1939.
MAGEE, H. E. (1945) *Proc. R. Soc. Med.*, **38**, 388.
MARSH, H. (1937) *J. Amer. med. Ass.*, **91**, 88, 330.
MacCALLUM, F. O. (1946) *Proc. R. Soc. Med.*, **39**, 655.
——, and BRADLEY, W. H. (1944) *Lancet* (ii), 228.
MacNALTY, A. S. (1937) Annual Report C.M.O. Ministry of Health.
Ministry of Health (1943) *Lancet* (i), 83.
—— (1945) *Lancet* (ii), 116.
MORGAN, H. V., and WILLIAMSON, D. A. J. (1943) *Brit. Med. J.* (i), 750.
PROPERT, S. A. (1938) *Brit. Med. J.* (ii), 677.
SAWYER, W. A., MEYER, K. F., BAUER, J. H., PUTNAM, P., SCHWERTKER, F. F. (1944) *Amer. J. Hyg.*, **39**, 337; **40**, 35.
SERGIEV, P. G., TAREEV, E. M., GONTÆVA, A. A. *et al.* (1940) *Terap. Arkh.* **18**, 595.
STAGSVOLD, L. (1938) *Norsk VetTidsskr.*, **50**, 69.
THEILER, A. (1919) *Rep. Vet. Res. S. Afr.*, **5**, 7.