and disorders of digestion and excretion, circulation and respiration. I can only pause to ask you to let your thoughts turn for a moment, in a tribute of respect, to a great British master in that field, Sir Charles Sherrington, born only six years after the Great Exhibition, and still living to see the spreading influence of his work, his teaching, and his example on all modern progress in our knowledge of the normal workings of the nervous system and of departures therefrom.

To-morrow *

Looking more widely at the position and the progress of effective medical knowledge as a whole to-day, I see no sign that the rate of its advance is becoming slower, that it is yet approaching anything like a climax or the crest of a wave. Everything seems, on the contrary, to point to its continuing, even with an increasing acceleration, into any to-morrow that we can foresee. If I gave rein to my imagination I might easily find myself involved in all kinds of prophetic fantasies. But I think that I ought rather to use the few minutes which are left to me in asking you to consider what we are going to do to-morrow, with all this new and potentially life-saving knowledge which is pouring now, and will continue to pour in a swelling flood, from the laboratories and the clinics. It must surely be a matter of first concern to us who are medical men, and not only to us but also to the members of the public whom many of you serve as your patients, to be assured that all this new knowledge, without avoidable delay, can be put to its proper use for the common good, for the saving of life, the assuagement of suffering, whether bodily or mental, and the promotion of the general health.

I am no politician myself, medical or otherwise; but it has seemed obvious to me for some time that the cost and the organization of all that would be needed for the fulfilment of that purpose would become too great a task for unaided individual enterprise in medical practice, and that the State would sooner or later have to give its assistance to enable that need of the community to be met. The State has supported medical research in this country since 1913, and is doing so to-day on a scale more than 30 times as great as that with which it began. I have heard no suggestion that this expenditure is too great or has been ill applied. And, since our State has assumed this predominant responsibility for supporting medical research, it was not unnatural, I think, to expect that support would also, in due course, be forthcoming from the State, to enable the wealth of new knowledge resulting from the medical research of all the world to be brought progressively to the aid of everybody needing it. Speaking in this Great Hall, I cannot be unaware of the many personal and professional difficulties and hardships entailed by a rapid adjustment to the new structure of medical practice which State action has now created and imposed. I am neither unmindful of these nor unsympathetic. But it seems to me that the success of whatever solution to these problems may be found must, in a longer view, be measured by the degree to which it will ease the all-important task of bringing the new and ever-growing resources of medical knowledge to the service of the individual patient and the community. It is by its success or its failure in meeting that, its primary obligation, that our National Health Service must stand to be judged at the bar of history; and we must wait for To-morrow to give the verdict.

HOMOLOGOUS SERUM HEPATITIS AND MEASLES PROPHYLAXIS

A REPORT TO THE MEDICAL RESEARCH COUNCIL

BY

W. CHAS. COCKBURN, M.B., D.P.H.

JOHN A. HARRINGTON, M.D., D.P.H.

(From the Central Public Health Laboratory,
Colindale, London)

REGINALD A. ZEITLIN, M.R.C.S., L.R.C.P.

(From the South London Blood Transfusion Depot,
Sutton, Surrey)

DAVID MORRIS, M.R.C.P., D.C.H.

Lately Paediatric Registrar, Prince of Wales's Hospital,
Tottenham

AND

FRANCIS E. CAMPS, M.D.

Lecturer in Forensic Medicine, London Hospital

Since the report by the Chief Medical Officer, Ministry of Health (Report, 1938), and by medical officers of the Ministry (Memorandum, 1943) of 52 cases of jaundice and nine deaths among children who received convalescent measles serum or normal adult serum for the prophylaxis and attenuation of measles, it has been shown that homologous serum hepatitis is not infrequently associated with the parenteral inoculation of apparently normal whole blood and blood products. Findlay and MacCallum (1937, 1938) described cases due to the use of small amounts of human serum in yellow fever vaccine, and outbreaks due to the same cause were noted by Fox *et al.* (1942) in Brazil. Beeson *et al.* (1944) reported 101 cases in 266 soldiers inoculated with mumps convalescent serum. Beeson (1943), Morgan and Williamson (1943), and Bradley, Loutit, and Maunsell (1944) published records of cases in persons who had been transfused with whole blood or pooled plasma, and numerous reports have since appeared, including detailed follow-up investigations of groups of transfused persons by Spurling, Shone, and Vaughan (1946) and Lehane *et al.* (1949) in Britain, and by Brightman and Korns (1947) in the United States of America.

Apart from the outbreak described by the Ministry of Health, however, we have not found in the literature any other cases due to the administration of adult serum or plasma to measles contacts. In the London County Council, over a period of more than 10 years up to 1943, 366 litres of convalescent measles serum and normal adult serum from over 3,000 donors were used to inoculate 36,000 contacts, most of whom were followed up after an interval of two months or more from the date of inoculation. No cases of jaundice were found (Memorandum, 1943). In addition, 30,000 children were inoculated with normal adult serum in 5-10 ml. doses between 1940 and 1949; the serum was issued through the Emergency Public Health Laboratory Service and the Public Health Laboratory Service. No reports of hepatitis following these inoculations were received, but no specific follow-up inquiry was made. Cases may have been missed, however; Bradley and his co-workers mentioned that the cases they reported would not have been associated with the previous injection of plasma if attention had not been drawn to the relationship during

a subsequent intensive follow-up for other reasons; and in three of the cases to be described here the injection of the plasma would not have been related to the hepatitis but for the careful routine inquiries made about all children inoculated.

It is therefore impossible to estimate accurately the risk of homologous serum hepatitis following the use of normal adult serum or plasma for measles prophylaxis. There is more information on the risk associated with transfusion. Spurling, Shone, and Vaughan found that 7.3% of 1,054 recipients of pooled plasma or serum subsequently developed jaundice attributable to the transfusion; Lehane, in a follow-up of 4,430 patients, calculated that 11.9% of recipients of large-pool plasma, 1.3% of recipients of small-pool plasma, and 0.8% of persons receiving whole blood were affected; and Brightman and Korhs have reported that 4.5% of 649 persons developed jaundice after transfusion with dried pooled plasma.

Age Incidence

Little information on age incidence was given in the Chief Medical Officer's report or in the elaboration of his report by medical officers of the Ministry of Health. Fatal cases occurred in children aged 10 months, 4 years, 7 years, and 13 years; otherwise it was merely stated that the cases were in young children, but that they included some boys of public-school age and one man of 61. For information on age incidence, therefore, it is necessary to refer to the surveys of post-transfusion hepatitis mentioned above.

In Lehane's series only one case, in a child aged 9 years, was noted in 214 children under 10 years transfused with whole blood, pooled plasma, or with a combination of these; for the succeeding 10-year age groups up to 80 years the attack rates in persons transfused with plasma alone or with plasma and blood were 5.7%, 6.8%, 7.1%, 9.1%, 9.3%, 8.1%, and 2.2% respectively. Brightman and Korhs, in their follow-up of 649 transfused persons, found no case of jaundice among 78 persons below the age of 20 years, 7 (2.2%) in 319 persons aged 20-49, and 22 (8.7%) in 252 persons aged 50-89. The incidence of hepatitis after transfusion in children under 5, therefore, is considerably less than in higher age groups. Similar findings were reported by Fox *et al.* (1942) and by Oliphant *et al.* (1943) in their yellow fever vaccine investigations, and Neefe and Stokes (1945) stressed the relative resistance of children under 5 years to homologous serum hepatitis and to infective hepatitis.

Mortality

The proportion of fatal cases has varied in different episodes. The medical officers of the Ministry of Health reported 41 cases with 8 deaths out of 109 children inoculated with a single batch of convalescent serum (case fatality rate, 19.5%); Brightman and Korhs reported 29 cases with 4 deaths (case fatality rate, 14%); and Bradley and his co-workers reported no deaths among 42 cases in 75 persons who were either transfused or skin-tested with an icterogenic batch of plasma.

Causal Agent

Homologous serum hepatitis has been shown (MacCallum and Bauer, 1944; Neefe *et al.*, 1944) to be transmissible to volunteers by parenteral injection of filtered serum or plasma from cases of the disease. It has also been shown that the icterogenic agent is resistant to heat at 56° C. for one hour, to 0.25% phenol

for 14 months, to other disinfectants, and to triple ether extraction at -20° C. (MacCallum, 1946).

The period between the inoculation of icterogenic serum and the onset of symptoms has varied. In most of the cases described, symptoms occurred from 50 to 150 days after injection, but some cases have been reported after 30 days and others after 196 days.

Present Episode

During 1947-9 an investigation was carried out on behalf of the Gamma Globulin Conference of the Medical Research Council into the value of gamma globulin, prepared by ether fractionation of human plasma (Kekwick and Mackay, 1949), in the prevention and attenuation of measles in susceptible contacts. A series of trials were arranged in different areas in which one-half of the contacts were treated with parenteral gamma globulin while the other half were given 5 ml. of normal adult serum or plasma. This plan was adopted after careful consideration of the risk involved. In view of the low incidence of homologous serum hepatitis in children under 5 years, and of the absence of reports of cases following measles prophylaxis during the ten years prior to this investigation, the use of adult serum was felt to be justifiable, particularly as in 1947, 644 deaths from measles were reported in England and Wales (Report, 1948).

In the investigation, 464 children were given globulin and 457 children adult serum. Gamma globulin was shown to be effective for the modification or prevention of the disease (Report, 1950), but, as it was apparent that adequate supplies of globulin could not be made available for some years at least, a small series of trials were set up in which the treated group were given dried human plasma reconstituted in a small volume of fluid instead of gamma globulin and the controls were given 5 ml. of unconcentrated adult serum as before. This method has already been described by other workers (McGuinness *et al.*, 1943; Wilson, 1950, personal communication) and found to be effective for modification of the disease.

In the course of this second investigation a batch of plasma, subsequently found to be icterogenic, was inocu-

TABLE I.—Homologous Serum Hepatitis. Children Given Dried Plasma (Lister) Batch L.P. 309

Case No.	Age (in Months) and Sex	Date of Inoculation	Dose	Date of Onset of:		End-result
				First Symptoms	Jaundice	
1	23 M	10/5/49	5 ml.	12/7/49 (62 days)	19/7/49	Recovered
2	29 F	10/5/49	5 "	—	—	No illness
3	18 F	10/5/49	5 "	—	—	—
4	39 M	11/5/49	10 "	10/7/49 (60 days)	11/7/49	Recovered
5	26 M	11/5/49	10 "	14/7/49 (64 days)	23/7/49	"
6	42 M	1/7/49	30 "	29/8/49 (59 days)	31/8/49	Died 7/9/49
7	40 M	1/7/49	30 "	2/9/49 (63 days)	Subicteric	" 7/9/49
8	42 F	1/7/49	30 "	27/8/49 (57 days)	2/9/49	" 9/9/49
9	45 M	1/7/49	30 "	28/8/49 (58 days)	1/9/49	Recovered
10	49 F	1/7/49	30 "	—	—	No illness

Figures in brackets indicate the incubation periods. * Reconstituted in 5 ml. of fluid.

lated into 10 children in varying doses (Table I). Within 57 to 64 days after inoculation seven of the ten children developed hepatitis and three of the seven died. A clinical feature of special interest was the occurrence of neurological symptoms without clinical jaundice in one

of the cases (Case 7). There was no doubt that the batch of plasma used—Batch L.P. 309—was icterogenic; the children were inoculated in three nurseries on different days, and no other cases of hepatitis occurred in children inoculated with other batches of plasma in the same nurseries at the same time. In three of the cases the association with the serum would have been missed but for the routine follow-up of all children inoculated in the trials.

Case 1

A male aged 23 months had no history of previous ill-health. He was fit and well until 62 days after an inoculation with 5 ml. of dried plasma reconstituted with 5 ml. of sterile water. He then became vaguely "off colour." One week later he was slightly jaundiced but not particularly ill. He was nursed at home for three weeks without difficulty, and was then admitted to hospital, one month after the onset of symptoms, with otitis media and persistent jaundice. The jaundice was deep when he was admitted, but he did not appear to be an ill child. The liver was palpable two fingerbreadths below the costal margin, and apart from the otitis media there were no abnormal clinical signs. He was given a low-fat and high-protein diet, and the ear infection was successfully treated with intramuscular injections of penicillin. The jaundice gradually faded, and he was fit for discharge six weeks after admission.

Laboratory Investigations.—On admission:—Urine: albumin, a heavy trace; bile, +++; urobilinogen, ++; bile salts, faint trace. Blood: serum bilirubin, 6.4 mg./100 ml.; direct van den Bergh, +; thymol turbidity, 9 units; serum alkaline phosphatase, 9 units; haemoglobin, 94%; white cells, 6,600 per c.mm. (46% polymorphonuclears, 49% lymphocytes); plasma proteins, 6.74 g./100 ml. (albumin 4.2 g., globulin 2.55 g., ratio 1.65). Repeated examinations of the urine showed a gradual return to normal. Before discharge: urine normal; serum bilirubin, 0.5 mg./100 ml.; thymol turbidity test negative.

Case 4

A male aged 39 months was well until 60 days after an inoculation of 10 ml. of dried plasma reconstituted with 5 ml. of sterile water; he then became listless and refused food. Next day he was jaundiced, but his general condition had not deteriorated. He was nursed at home without difficulty until the tenth evening, when he suddenly collapsed and became semicomatose. The family doctor found him very irritable and restless; neck rigidity was present, the reflexes were all brisk, and the left plantar response was extensor. He was admitted forthwith to hospital as suffering from "jaundice and encephalitis." The admitting doctor described the child as ill, very irritable, and deeply jaundiced. The liver was palpable 1 in. (2.5 cm.) below the costal margin. There was no neck rigidity, and, apart from extreme irritability, there were no abnormal signs in the central nervous system. He was given a low-fat and high-protein diet, and made a full clinical recovery. He was discharged from hospital six weeks after admission.

Laboratory Investigations.—On admission:—Urine: albumin, +; bile salts and pigments, +; no urobilinogen. Blood: haemoglobin, 90%; red cells, 3,590,000 per c.mm.; white cells, 18,000 per c.mm. (38% polymorphonuclears, 58% lymphocytes); serum bilirubin, 5.5 mg./100 ml.; thymol turbidity, 15 units; serum alkaline phosphatase, 8 units; Takata-Ara test, ++-. No further biochemical tests were done. Before discharge: urine normal. Blood: haemoglobin, 95%; white cells, 8,450 per c.mm. (34% polymorphonuclears, 58% lymphocytes).

Case 5

A male aged 26 months was treated at home: he became ill 64 days after inoculation with 10 ml. of dried plasma reconstituted in 5 ml. of sterile water, and developed jaundice nine days later. He made a full clinical recovery.

Case 6

A male aged 42 months had a history of mild gastroenteritis in infancy. He had been quite well until 59 days after an inoculation with 30 ml. of dried plasma reconstituted with 5 ml. of sterile water, when he became vaguely "off colour," his temperature was 104° F. (40° C.), and a diagnosis of pneumonia was made. He was treated with sulphonamides. Two days later he became jaundiced. For five days he was nursed at home with difficulty, as he would not eat and was very restless and irritable. He was admitted to hospital one week after the onset of symptoms.

On admission he was mildly jaundiced, semicomatose, with phases of extreme restlessness in which he would utter piercing screams. These phases lasted from one to three minutes and occurred at varying intervals of from 20 to 60 minutes. The liver was palpable one fingerbreadth below the costal margin. There was no lymphadenopathy or skin haemorrhage. The pupils were dilated, and there was no reaction to light; the reflexes were all depressed; the fundi were normal. A diagnosis of "cholaemia" was made. He was given intravenously 5% glucose in normal saline alternating with "casydrol" (casein hydrolysate) and methionine 0.5 g. by stomach tube three times a day. The child's condition progressively deteriorated, and he died 36 hours after admission.

Laboratory Investigations.—Urine: albumin, heavy trace; bilirubin, ++; no urobilinogen or urobilin; no leucine or tyrosine crystals seen. Blood: white cells, 10,900 per c.mm. (74.5% polymorphonuclears, 24% lymphocytes, 5% large mononuclears); plasma proteins, 7.2 g./100 ml. (albumin 3.8 g., globulin 3.4 g., ratio 1.12); blood sugar, 96 mg./100 ml.; thymol turbidity, 20 units; serum alkaline phosphatase, 25 units; serum colloidal gold, 5; Takata-Ara test, ++-.

Case 7

A male aged 40 months had a history of middle-ear disease. He was quite fit and well till 63 days after an inoculation of 30 ml. of dried plasma reconstituted with 5 ml. of sterile water, when he was sick in the train while returning from a holiday. The next day he had a temperature of 102° F. (38.9° C.), and was treated by his own doctor for a "cold" and kept in bed. Four days after the onset of symptoms he became worse, had screaming attacks and epistaxis, and was admitted to hospital.

His temperature was normal, but he looked an ill child. Meningism was present, and it was considered that he might be suffering from polio-encephalitis or a subdural haematoma. Jaundice was not present. A lumbar puncture was performed and showed no abnormality. The blood culture was sterile. He was treated with penicillin, 250,000 units I.M., and "soluthiazole," 2 g. intravenously and 1 g. orally. He was also given 20 ml. of 50% glucose intravenously, but without effect, and he died 34 hours after admission. In view of the history of a fall when he struck his head whilst on holiday, the case was reported to the coroner.

Post-mortem Findings.—A well-nourished boy, height 3 ft. 2 in. (96.5 cm.). Slight icteric tinge of conjunctivae. Superficial abrasion outer side of left eye with slight bruising of the eye and small subconjunctival haemorrhage. No fracture of the skull. Slight discoloration of the dura mater in the left anterior fossa and some adherence of the dura to the left middle fossa. Some oedema of the meninges with hyperaemia, but no obvious naked-eye changes. Section of brain showed congestion only. Both lungs showed some oedema and congestion with subpleural haemorrhages. The myocardium was pale; there were pericardial haemorrhages and subendocardial haemorrhages on the septum. The stomach contained some altered blood. The liver was slightly enlarged and pale and showed areas of necrosis with some patchy haemorrhages. Microscopy showed massive necrosis of the parenchymatous cells with some isolated surviving liver cells in the portal areas with aggregation of lymphocytes.

Case 8

A female aged 42 months, with no history of previous illness, was quite well until 57 days after an inoculation of 30 ml. of dried plasma reconstituted with 5 ml. of sterile water, when she became vaguely ill, with loss of appetite and listlessness. Six days later she became jaundiced. She was nursed at home without difficulty until the day before admission, when she became drowsy, with intervals of restlessness and crying out.

She was admitted to hospital 11 days after the onset of symptoms. Her condition was similar to that of Case 6, but she was slightly more jaundiced and restless. The liver was only just palpable below the costal margin, the pupils were dilated and did not react to light, and the reflexes were all depressed. She was given an intravenous drip of 5% glucose in normal saline alternating with casein hydrolysate, but failed to respond, and died 30 hours after admission.

Laboratory Investigations.—Urine : albumin, heavy trace ; bile, +++ ; no leucine or tyrosine crystals seen. Blood : haemoglobin, 98% ; white cells, 17,500 per c.mm. (75.5% polymorphonuclears, 15.5% lymphocytes, 5% mononuclears) ; red cells, 5,200,000 per c.mm. ; plasma proteins, 7 g./100 ml. (albumin 4.4 g., globulin 2.6 g., ratio 1.7) ; thymol turbidity, 10 units ; serum alkaline phosphatase, 22 units ; Takata-Ara test ++- ; serum colloidal gold, 3.

Post-mortem Findings.—A well-nourished girl with well-marked jaundice of the skin and conjunctivae. Height 3 ft. 4 in. (102 cm.). The brain showed flattening of the convolutions with some hyperaemia of the meninges and a small haemorrhage on the surface of the right frontal lobe. There was some oedema, and bile-staining was not marked. Sections merely showed congestion. The lungs showed oedema with some peripheral collapse and haemorrhages on the posterior surface. The stomach showed stasis, and contained a small quantity of blackish fluid. The liver was not enlarged and was rather tough to cut ; microscopy revealed massive necrosis of the parenchymatous cells with many surviving liver cells in the proximity of the portal

areas. Some of these surviving liver cells contained masses of bile pigment. There were many regenerating bile ducts and aggregation of lymphocytes in some portal areas.

Case 9

A male aged 45 months, treated at home. He became ill 58 days after inoculation with 30 ml. of dried plasma reconstituted in 5 ml. of sterile water, and developed jaundice four days later. Recovery was clinically complete.

Source of the Plasma

The icterogenic pool of plasma came from a single bleeding session of 60 donors on February 8, 1949 ; all 60 donors were subsequently traced. The plasma was used for fractionation except for a small amount which was dried and issued unfractionated for measles prophylaxis.

Six of the donors, all women, had a history of jaundice in the past, the most recent five years and the most remote nearly 40 years before. Because it seemed probable that the offender would be found among them, these six donors were investigated in detail (see below).

No history of jaundice within the past two years was obtained from the remaining 54 donors in answer to the routine question asked at the time of bleeding in February, 1949. In September, 1949, all of them were asked to confirm that they had no history of jaundice in the past, however distant ; they were also asked whether they had had jaundice since their donation in February, 1949. (This covered a period of six months and ensured that none was incubating the disease at the time of donation.) All 54 replied to the questionnaire and confirmed their freedom from jaundice at any time.

It was considered impracticable to go more deeply into the question of possible contact with jaundice or of histories of minor pyrexial attacks in each of these

TABLE II.—Details of Blood Donations of Six Donors with a Previous History of Jaundice

Donor	Age and Sex	Jaundice	Blood Donations		Destination	Results of Follow-up
			Period	Amount (Bottles)		
1	58 F	As child	1942-7 1948 1949 (Feb.) 1949 (July)	5 1 1 1	Whole blood transfusion Icteric measles-plasma pool Fibrin foam	No records available No jaundice in recipient at January, 1950 —
2	58 F	24 years ago	1942-7 1947 1948 1948 1949 (Feb.) 1949 (Dec.)	5 1 1 2 1 1	Fibrin foam Fibrinogen and thrombin Fibrin foam Icteric measles-plasma pool Grouping serum	No records available No jaundice in 2 recipients at January, 1950 " " 4 " " " " 9 " " — Not used parenterally
3	47 F	5 years ago	1941-8 1948 1948 1949 (Feb.) 1949 (June)	11 1 1 1 1	Whole blood " " Icteric measles-plasma pool Whole blood	No records (3 bottles unused) Recipient died of general peritonitis within the hepatitis incubation period Recipient died of malignant disease within the hepatitis incubation period — No jaundice in recipient 6 months afterwards
4	45 F	9 years ago	1941-6 1947 1947 1948 1949 (Feb.) 1949 (Sept.) 1950 (May)	6 1 1 1 1 1 1	Whole blood " " Small plasma pool Icteric measles-plasma pool Whole blood " "	No records available Recipient died of pulmonary tuberculosis within a week Recipient not traced Remains unused — No records available 100 ml. transfused. No hepatitis 6 months afterwards
5	45 F	25 years ago	1943-8 1949 (Feb.) 1949 (Sept.)	6 1 1	Icteric measles-plasma pool Whole blood	No records available — No jaundice 6 months afterwards
6	55 F	43 years ago	1941-4 1947 1948 1949 (Feb.) 1949 (July)	7 1 2 1 1	Small-pool plasma Fractionation: Fibrin foam and fibrinogen Icteric measles-plasma pool Whole blood	No records available No jaundice in 3 recipients at January, 1950 " " 9 " " — No jaundice 6 months afterwards

54 donors; nor were the previous donations from each donor followed up. Further inquiry could be undertaken later if necessary. A sample of serum from all 60 donors was collected, and has been stored at -70°C . at the Virus Reference Laboratory, Colindale, for laboratory investigation if and when a suitable method is devised.

For the present report the follow-up was confined to the six donors with a past history of jaundice. In each case many donations had been made prior to February, 1949, and all six had given blood since that date. Each donation was followed to its final use as whole-blood transfusion, inclusion in large or small plasma or serum pools, or as plasma or serum fractions (fibrinogen, fibrin foam, or thrombin). Many of the earlier donations were made during the war and records were not available. The details of these donations are given in Table II.

Donors 3, 4, 5, and 6 gave blood for whole-blood transfusion after plasma pool L.P. 309 had been collected, and this was not followed by jaundice in the recipients. Had the virus been present in any one of them it is to be expected that the heavy inoculum would have been followed by infection, although it is, of course, quite possible that the virus might have been present in February, 1949, but absent in the subsequent transfusion; or, alternatively, that a high degree of resistance protected the recipient.

In donors 1 and 2 it was unfortunate, so far as the investigation was concerned, that the subsequent donations were used for the preparation of fibrin foam and grouping serum.

Inoculation of Gamma Globulin Prepared from the Same Pool of Plasma

While this episode was being investigated it was found that 103 3-ml. doses of gamma globulin prepared from the same pool of plasma, and designated Batch L.G. 309, had already been used by practitioners and hospitals for measles prophylaxis. It was obvious that this chance occurrence afforded an opportunity, which was unlikely to recur, of determining the safety or otherwise of gamma globulin prepared from an icterogenic batch of plasma, and a careful follow-up was organized. If Batch L.G. 309 had been used in the controlled investigation (see above), the follow-up would have presented few difficulties, but it happened that this particular batch had been allocated for issue to practitioners at a time when measles was epidemic and when detailed records were not always kept; despite this, a satisfactory follow-up of the recipients for six months after inoculation was carried out in co-operation with the practitioners concerned.

Method of Follow-up

As the validity of the findings depends on the effectiveness of the follow-up, the method adopted is described in detail.

Of the 103 ampoules prepared, 11 were either not issued from the laboratory or were returned unused; 92 ampoules had therefore to be accounted for. From the records of issue kept in the laboratory and from routine returns from practitioners, it was known that 28 persons had each received one ampoule and that 17 persons, each of whom had been given more than one dose, had been inoculated with a total of 51 ampoules. The recipients of 79 ampoules were therefore readily identified. Although the records were not complete, there

was very strong circumstantial evidence that five other persons had each received one ampoule of this batch. This left eight ampoules, about the use of which there was no exact record. It was known that Batch L.G. 309 was issued from the laboratory within the period May 5–20, 1949. All issues of gamma globulin during May were therefore checked, and in the majority evidence was obtained that the recipients had not been inoculated with Batch L.G. 309; but in 24 instances the record of the batch numbers could not be found. It was thought reasonable to assume that the eight ampoules of Batch L.G. 309 not accounted for had been employed in the immunization of some of the 24 persons concerned, and all 24 were followed up for six months after inoculation (see Table III).

TABLE III.—*Disposal of Gamma Globulin (Lister) Batch L.G. 309, Prepared from the Same Parent Batch of Plasma as L.P. 309*

No. of 3-ml. ampoules of L.G. 309 prepared	103	
No. of 3-ml. ampoules of L.G. 309 not issued or returned unused	11	
No. of 3-ml. ampoules of L.G. 309 issued and used by general practitioners and hospitals	92	
Category of Recipient	No. of Recipients	No. of Ampoules Used
Received one ampoule	28	28
Received two or more ampoules	17	51
Total number of persons known to have received L.G. 309	45*	79
No. of persons who from date of issue and other evidence very probably received batch L.G. 309	5	5
†No. of persons inoculated between May 5 and 20, 1949, who may or may not have received batch L.G. 309	24	8

* Two of these, each of whom received one ampoule, could not be traced.

† These almost certainly include the persons who received the remaining 8 ampoules of L.G. 309 which could not be traced as the batch number was not noted when the inoculation was given.

As the persons inoculated were widely scattered throughout England, we enlisted the help of the general practitioners and hospital officers to whom the globulin had been issued. A full explanation of the circumstances was sent to those concerned, and they were asked to visit the recipients at intervals until six months had elapsed, and to complete a form giving details of jaundice, of symptoms suggestive of subicteric attacks, or of any other illness in the period. In some instances the observations were made by one of us (J. A. H.) or by a health visitor. Whole-hearted co-operation was given by the doctors concerned, and all but two children, each of whom was known to have received one ampoule of Batch L.G. 309, were kept under observation.

Result of Follow-up

From Tables IV and V it is apparent that the recipients were in a wide age range, and that the doses were also varied. Twenty persons were over 5 years of age; four of these were adults each of whom had been given 9–30 ml. Records of the age incidence of homologous serum hepatitis previously mentioned suggest that susceptibility increases with age and, as 7 out of 10 children under 5 developed severe hepatitis when inoculated with the parent batch of plasma, a higher attack rate in the recipients of the gamma globulin would have been expected if the gamma globulin had been equally icterogenic.

In fact, however, only one case of hepatitis with jaundice occurred and there was no evidence of sub-icteric attacks.

The single case was in a boy aged 12 years who was known to have received 8 ml. of gamma globulin from

TABLE IV.—Age and Sex Distribution and Result of Follow-up of Persons Who Are Known to Have Received Gamma Globulin Batch L.G. 309

Age Group (in Years)	Persons who Received 3 ml.			Persons who Received more than 3 ml.				Total
	M	F	Result of Follow-up	M	F	Dose	Result of Follow-up	
<1 ..	1	—	No hepatitis	—	1	6 ml.	No hepatitis	2
1- ..	6	3	"	1	3	6 "	"	13
2- ..	1	8	"	—	1	6 "	"	10
3- ..	3	1	"	—	—	6 "	"	4
4- ..	—	1	"	—	—	6 "	"	1
5- ..	1	1	"	3	3	6 "	"	8
10- ..	—	—	"	1	—	8 "	Hepatitis	1
20- ..	—	—	"	—	1	9 "	No hepatitis	1
30-40 ..	—	—	"	3	—	30 ml. (1) 24 " (1) 9 " (1)	"	3
Total ..	12	14	No hepatitis	8	9	Dose range 6-30 ml.	1 case of hepatitis	43

TABLE V.—Age, Sex Distribution, and Result of Follow-up of Persons who were Inoculated with Gamma Globulin which was Probably Batch L.G. 309

Age Group (in Years)	*Persons who very probably received Batch L.G. 309			†Persons who may or may not have received Batch L.G. 309		
	Male	Female	Result of Follow-up	Male	Female	Result of Follow-up
<1 ..	1	1	No hepatitis	3	1	No hepatitis
1- ..	—	3	" "	1	—	" "
2- ..	—	—	" "	2	3	" "
3- ..	—	—	" "	4	2	" "
4- ..	—	—	" "	1	—	" "
5- ..	—	—	" "	2	2	" "
10- ..	—	—	" "	1	2	" "
Total ..	1	4	No hepatitis	14	10	No hepatitis

* Persons in whom there was strong circumstantial evidence that they had received L.G. 309.

† Includes 14 persons on whom 5 ampoules of L.G. 309 were known to have been used but of whom there is no record of which of them received the inoculation, and 10 persons who were inoculated with gamma-globulin which may or may not have been L.G. 309.

Batch L.G. 309 and who developed symptoms 74 days afterwards. He complained of anorexia and abdominal discomfort, and on examination by his family doctor was found to have a rise of temperature and to be slightly but definitely jaundiced. As the illness was mild he was treated at home, and was confined to bed for three weeks; the length of stay in bed was influenced more by the fact that he was convalescent from acute rheumatism than by the severity of hepatitis. Jaundice was present for a few days only and the urine was bile-stained for 10 days: recovery was clinically complete.

This boy had been exposed to measles while in hospital with acute rheumatism and was inoculated 57 days before discharge from hospital. He had received no other inoculations for six months before his illness, and during his stay in hospital he had been treated with salicylates and "anthisan" (mepyramine hydrogen maleate) only. The gamma globulin was given by intramuscular injection; it was not always the custom in the hospital to use a fresh needle or syringe for each inoculation, but on the particular day on which he was given gamma globulin he was the only patient to be injected. Syringes and needles were boiled daily and kept in 70% alcohol, and the syringe in question was probably used in another case on the previous day for the intramuscular administration of penicillin. The boy developed jaundice 17 days after discharge from hospital.

Questioning of the household contacts failed to reveal any history of jaundice, and two months after the boy's illness no secondary cases had occurred in his family.

Fifty-six children, who were ward contacts of the child during the 40 days before the onset of jaundice and were subsequently discharged from hospital, were visited in their homes. None was found to have had jaundice during the six months prior to the date of the visit. The records for children admitted to the ward over a four-months period before the boy's discharge showed that no cases of infective hepatitis had been admitted, and, so far as could be ascertained, there were very few cases of the disease in the area during this time. There were no cases of hepatitis among the nursing staff or ward orderlies. Ward visitors were permitted to see the children, but they could not be traced.

Discussion

In the absence of laboratory and clinical methods of distinguishing homologous serum hepatitis from infective hepatitis, deductions in a follow-up of this nature must be made on the epidemiological evidence. The occurrence of a single case of mild jaundice out of 58 persons inoculated, 74 days after the administration of gamma globulin prepared from a known icterogenic batch of plasma, cannot be ignored, but it compares favourably with seven cases of jaundice and three deaths in ten persons inoculated with the unfractionated plasma. After intensive investigation, *no epidemiological evidence to suggest a diagnosis of infective hepatitis* was found among the contacts of the case which occurred after inoculation of gamma globulin; there was no evidence to incriminate drug therapy or syringe technique, and it must be assumed that the case was due to the administration of the gamma globulin.

Ordman *et al.* (1944) found only one case of jaundice among 400 persons inoculated with gamma globulin. They did not attribute this case, which occurred three months after inoculation, to the inoculation, as 74 other children who received injections from the same batch were unaffected. Janeway (1945) followed up 869 persons inoculated during 1943-4 without finding any who developed hepatitis. Gamma globulin can therefore be considered to be much less icterogenic than plasma or serum; but, in view of the episode here described, it is probable that it is not wholly free from the risk of causing hepatitis.

It has been stated that the size of the inoculum of icterogenic material has, within certain wide limits, no effect on the attack rate, incubation period, or severity of the disease, though different pools of proved icterogenicity have different attack rates (MacCallum, 1946); in support of this contention homologous serum hepatitis has been observed to follow the injection of as little as 0.1 ml. used as a skin test for sensitivity, but the injection of as much as 1.5 litres of the same batch of icterogenic plasma given as a transfusion produced cases of equal severity (Bradley *et al.*, 1944).

The suggestion that dosage does not influence the attack rate or severity of the disease is not supported by the evidence presented in this paper, though the numbers are small. Out of five children who received 30 ml. of icterogenic plasma, four developed jaundice and three died. Both children given 10 ml. developed jaundice and recovered, and only one of three children given 5 ml. developed the disease.

Case 7 is of interest because only neurological symptoms and signs were noted during life, jaundice being

apparent only after death. A similar picture was seen by one of us (F. E. C.) in a small outbreak of infective hepatitis in 1944:

Case A.—A woman aged 21 was admitted to hospital with a history that six days previously she had had intermittent frontal headaches and vomiting. After admission she vomited altered blood, looked toxic, but was not jaundiced. She became progressively worse, coma ensued, and she died without any jaundice developing. Post-mortem examination revealed advanced hepatic necrosis, which was less severe at the centre of the lobules. Sections of the brain showed no abnormality.

Case B.—A woman aged 24 had pains in the arms and legs and vomiting of brown material seven days before admission. On admission she complained of abdominal tenderness and sternal pain. Five hours later she became manic, restless, irritable, and completely uncooperative. There were no abnormal signs in the central nervous system. Just before death there was a faint jaundice, spasticity of the legs, and the plantar responses were extensor. She died in coma. Post-mortem examination showed severe liver necrosis but no changes in the brain.

In a certain number of cases of severe liver damage of rapid onset it is clear that the predominant picture may be one of cerebral irritation, death intervening before the clinical appearance of the jaundice. Bradley (1950, personal communication) examined the protocols of 50 deaths from hepatitis and found that in 10% neurological symptoms appeared before the jaundice.

Summary and Conclusions

Of 10 recipients of the same batch of plasma for measles prophylaxis, seven developed a severe form of jaundice and three of the seven died. One of the patients who died had symptoms of encephalitis without apparent jaundice. Five cases are described in detail.

Part of the same parent batch of plasma was fractionated and gamma globulin was prepared from it. In the follow-up of 56 out of the 58 recipients of this batch of gamma globulin, only one mild case of jaundice occurred: in a boy aged 12 who had received 8 ml. In the absence of evidence to the contrary, this case must be considered to be one of homologous serum hepatitis resulting from the administration of gamma globulin prepared from a batch of plasma subsequently shown to be icterogenic.

Of the 60 donors who gave blood to the pool, six who had a previous history of jaundice were investigated in detail. No evidence that they were the source of the infection was obtained.

Care in recording the batch numbers of human blood and its products materially assisted in investigating the origin of the contaminated batch.

The risk of homologous serum hepatitis following parenteral inoculation of gamma globulin prepared from an icterogenic pool of plasma appears to be much less than that following the use of unfractionated plasma, but it cannot be ignored.

Children under 5, who have been held to be relatively insusceptible to homologous serum hepatitis, may in certain circumstances develop the disease, which may prove fatal.

Owing to the long incubation period, cases of homologous serum hepatitis may readily be missed, and in all cases of jaundice a history of previous injections should be inquired into.

In some cases with rapid liver damage the patients may show predominantly neurological symptoms with no apparent jaundice during life.

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The Edinburgh Royal (Dick) Veterinary College is no longer independent; it was embodied within the University in May. Founded in 1823 by William Dick—whose name was incorporated in the title of the college to distinguish it from a later rival—the college has long been an important centre for the teaching of veterinary medicine. The son of a farrier, William Dick decided when he was very young that there was a great need for a veterinary school. At the end of the eighteenth century the farriers would treat sick horses as well as shoeing them—very often with little or no knowledge of the aetiology or proper treatment. Dick attended lectures given by Dr. John Barclay, of the Edinburgh Medical School, and in 1817 obtained his diploma from the London Veterinary College after only three months' studying. The Highland Society appointed him lecturer in veterinary medicine, and in November, 1823, when he gave his first lecture, the college was founded and 25 students attended during the first session. From the beginning, instruction in shoeing was given at Dick's house, and many of the lectures as well. The school premises, until new ones were taken in Clyde Street, consisted of a forge, a stable used as a temporary hospital for sick animals, a tiny museum, and a lecture room "fitted up with rough deal planks set upon rough props; seats rising tier above tier, until your head touches the top of a very dark coloured ceiling." The cost of the new buildings was £2,500 and was borne entirely by Dick himself with the exception of a grant of £50 from the Highland Society towards the equipment of the lecture room. Dick left all his money to the college when he died in 1866, and the City Corporation administered the college as his trustees. After a varied history during the next 60 years the college became more and more closely associated with the university, and is now the official University Veterinary School. A fuller account appeared in the *Scotsman*, June 1.