Special Articles

HOMOLOGOUS SERUM JAUNDICE

MEMORANDUM PREPARED BY MEDICAL OFFICERS OF THE MINISTRY OF HEALTH

BETWEEN Aug. 13 and Sept. 1, 1885, 1289 persons employed in a shipbuilding yard in Bremen were vaccinated with "glycerinated humanised" lymph and of these 191 developed jaundice after an incubation period of several weeks. In two other groups of 87 and 500 workmen in the same yard vaccinated at the same time with different lymph there were no cases of jaundice (Lurman 1885).

During 1937, 41 of 109 recipients of a single batch of measles convalescent serum administered subcutaneously developed jaundice and 8 died. These cases were scattered proportionately over a wide area in the South of England. A batch of measles adult serum, pooled and Berkefeld candled in the same laboratory, gave rise to at least 11 cases of jaundice with one death. Other batches of measles serum were also suspect (Annual Report of the Chief Medical Officer 1937).

In the same year a similar sequence of events was reported in persons receiving yellow fever vaccine subcutaneously (Findlay and MacCallum 1937) and since then the icterogenicity of certain lots of yellow fever vaccine has been demonstrated repeatedly. In Brazil in 1939, 187 lots of vaccine were used to immunise 1,300,000 people. One of these lots was followed by jaundice in 304 persons, an attack-rate of 27%. The vaccine contained human serum, and although for a time change in the seed virus appeared to eliminate the causal factor, it reappeared in 1940, when two of 78 lots of vaccine caused attack-rates of jaundice of 7·66% and 1·56%, with fatalities of 2·58% and 2·00% respectively among 19,191 persons immunised. Other lots of vaccine were also mildly icterogenic (Fox et al, 1942). During the first six months of 1942, 28,585 cases of jaundice appeared in American troops who had had yellow fever vaccine containing human serum; 62 died (Editorials 1942).

In March, 1942, 266 British troops were each given less than 14 c.cm. of Seitz filtered pooled mumps convalescent plasma in one or two doses intravenously; 86 of them developed jaundice (Chesney, Gordon, Hawley, MacFarlane and Stegman, unpublished communication).

Of 36 patients treated at an EMS hospital with massive transfusions of Seitz filtered pooled and dried human serum for various forms of peripheral vascular disease (Hayward 1942, Hayward and Jordan 1942) 8 are known to have developed jaundice (Morgan and Williamson, unpublished communication).

Full details of the yellow fever vaccine incidents have been published and a recurrence prevented by eliminating human serum from the vaccine. Reports on the mumps convalescent serum and the transfusion cases, which are still under investigation, are promised by the observers. The measles convalescent serum story, now six years old, was not published in detail, and, since in the light of recent events it assumes a greater importance, the following account has been reconstructed from the contemporary records.

Measles Serum Hepatitis

Epidemic (catarrhal) jaundice was known to have occurred sporadically among school-children in a county town during 1936, and inquiry of all practitioners brought to light 53 cases between March, 1935, and March, 1937. During the same period 185 children in the town had received measles serum from one and the same laboratory, 110 of them before Feb. 10, 1937, on which day a new batch of serum which will be referred to as K60 came into use. The 110 remained well, but among the remaining 75, 18 developed jaundice 16–114 days later and 4 died of hepatic necrosis, from which cause there were no other deaths in the city. The injections associated with jaundice were given during the period Feb. 16 to March 31, and although in 11 of them only was the measles serum batch number recorded all 18 patients probably received K60.

At a small preparatory boarding-school of 80 boys in an adjacent county 7 boys exposed to measles in the same dormitory were given K60 serum on Feb. 9, 1937; 4 of them developed jaundice (3 severely ill) about 66 days later. Only one other boy, who had returned to school late and was in a different dormitory, received serum. This was on March 4. The boy became ill 61 days later and was the only other case of jaundice in the school.

These events in themselves were not beyond the bounds of coincidence. Multiple deaths in a family during attacks of non-spirochætal hepatitis are recorded (Bulmer 1923, Symmers 1920, Hirschberger 1936), and epidemic jaundice is a very common disease in communities. For example, in the five years 1930–34, in 21 boys' and 10 girls' residential schools jaundice occurred in all but one of the boys' schools and all but 3 of the girls' schools (MRC Special Report 1938). But while these events were being investigated news was received that in a county institution 100 miles or more away 7 of 8 mentally deficient children injected with K60 on June 1, 1937, became ill on an average 82 days later (in August); 6 of them had jaundice and 3 died. There were 42 children in this community among a total of 541 inmates and 94 staff. The children were divided by an outbreak of dysentery in January, 1937. Measles first appeared in the diarrhœa-free group in April but did not invade the dysentery group until May 24. It may therefore be assumed that the 11 members of the dysentery group who remained on June 1 were reasonably well isolated. None of the 8 inoculated had left this group since it was formed, although 4 of the other patients and the nursing staff had been in contact with the outside world. It is known beyond doubt that there was no antecedent or concurrent infective hepatitis in the institution and the case against K60 might have been complete but for the fact that jaundice appeared in 2 uninoculated children in the dysentery group in the following November (Propert 1942).

Batch K60 was pooled measles convalescent serum amounting to 880 c.cm. derived from 26 donors residing in four localities and collected by four practitioners during April, 1936. It was candled and treated with 0·5% of an equal mixture of phenol and ether before being bottled in 171 phials; 121 of these phials were distributed between April, 1936, and June, 1937, in nine localities scattered over a wide area in the South and East of England, and 82 persons were certainly, and a further 27 probably, inoculated with it. Of the 109 recipients, 41, proportionately scattered over the nine localities, subsequently became ill, 37 with jaundice; 8 died—a phenomenally high fatality of 12%—and, more significantly, they all died between the 61st and 93rd day after receiving serum.

All unused serum of the batch (K60) had been recalled by November, 1937, and the laboratory has not issued measles convalescent serum since the middle of 1938. This laboratory is beyond reproach both structurally and so far as its technique and staff are concerned, and has had long experience in handling serum and similar biological products. The proprietors provided comprehensive information concerning the distribution of measles serum, and a specific inquiry disclosed numerous other cases of jaundice following the administration of certain other batches of serum from the laboratory. At Leeds (Jervis 1939) 9 batches were employed to protect 158 children during 1936, 1937 and 1938, and jaundice appeared four weeks to four months later in 23 children receiving serum from 5 of the 9 batches. Careful survey covering the same three-year period brought to light only 309 cases of epidemic hepatitis scattered throughout the city. Different sets of donors contributed to each batch of measles serum, yet 2 of the batches appeared to be more hepatotoxic than the others and one of these, K488, is believed to have given rise to jaundice elsewhere, including a South coast town, where of 130 c.cm. received 58 c.cm. was injected into 14 children, 6 of whom subsequently developed jaundice and one died.

Hepatitis following measles serum therefore occurred among persons who were for the most part young children recently exposed to measles. It included, however, some boys of public-school age and one man of 61. The sexes were evenly represented. The Registrar-General reported that during the period 1926–36 there was no increase in the total mortality from all diseases of the liver and gall-bladder (excluding tumours or gallstones), in children under 15 years. During the period Jan. 1,

1937, to July 9, 1938, there were 62 deaths. In 15 of these cases a biological product had been administered at some time before the onset of jaundice, in 6 more than a year previously and in 9 between two and four months before death. Of these 9, 7 had received either K488 or K60 measles serum.

CLINICAL FEATURES

Unfortunately, as is to be expected when special interest is aroused only long after the event, very few clinical notes are available. In addition there is the difficulty of judging whether serum from any given batch was or was not a factor in the subsequent development of jaundice. Only with regard to two batches, K60 and K488, did suspicion amount to strong probability, and for this reason a discussion of the clinical features must be confined to the notes on 34 cases associated with these batches in which the story goes beyond a diagnosis of "hepatitis" or "jaundice." The number of times certain signs and symptoms are mentioned in these 34 histories is shown in table I.

TABLE I—SIGNS AND SYMPTOMS RECORDED IN MEASLES SERUM HEPATITIS

—	Recovered		Deaths		Total
	K60	K488	K60	K488	
Records available	20	5	8	1	34
Malaise	2	..	1	..	3
Anorexia	..	..	3	..	3
Tiredness, depression	2	..	1	..	3
Irritability, restlessness	2	..	7	1	10
Screaming	1	..	4	..	5
Intractability	1	..	5	..	6
Nausea	1	..	..	..	1
Vomiting	10	1	7	1	19
Constipation	1	..	3	..	4
Loose stools	1	..	1	..	2
Jaundice	15	5	7	1	28
Bile in urine	2	1	2	1	6
Clay-coloured stools	1	1	1	1	4
Liver palpable	6	1	2	..	9
Abdominal pain	2	..	1	..	3
Hæmatemesis	2	..	6	..	8
Convulsions	..	..	4	..	4
Tetany	..	..	1	..	1
Delirium	4	..	3	..	7
Extensor plantars	1	..	2	..	3
Squint	..	..	1	..	1
Temperature normal	1	..	3	1	5
Temperature elevated	5	..	4	..	9
Pulse normal	2	..	3	..	5
Bruising	..	..	2	..	2
Urticaria	1	1	3	..	5

Except for the mention of irritability, restlessness, intractability, screaming and delirium, and the occurrence of urticaria and extensor plantar responses, this list does not suggest a diagnosis other than epidemic hepatitis or catarrhal jaundice in the recovered cases, and the infrequent mention of clay-coloured stools may easily result from inadequate record. The long interval between onset of symptoms and appearance of jaundice in some cases was of interest.

Day of disease	1	2	3	4	5	6	7	Later
Recovered	1	..	3	1	..	1	1	1 on 12th day
Died	..	..	2	1	2	..	..	1 on 40th day
								1 on 16th day
Totals (15)	1	..	5	2	2	1	1	3

FATAL CASES

Those who died exhibited some unusual features which are best presented in the words of the contemporary histories.

CASE 1.—A girl, aged 13 years, received 10 c.cm. of K60 between March 25 and 30, 1937; 53 or 58 days later, on May 22, developed violent urticaria; temperature normal. *2nd day:* confirmed in church; felt a little queer afterwards. *3rd day:* evening temperature 100·2° F.; seen by doctor who could make nothing of her but vaguely thought of measles. *4th day:* evening temperature 104° F. but no signs or symptoms except constipation and violent dislike for food. *5th day:* slightly jaundiced but not thought to be ill; in evening became very restless and noisy and did not recognise her mother. *6th day:* temperature normal in morning; restless; requiring to be kept in bed; once rolled on the floor calling out "Oh dear, oh dear" and could not be quietened; doctor thought her liver dullness was less and that he had missed an appendix; consultant saw her and diagnosed acute yellow atrophy; gums bled, passed blood in stool, became unconscious and went downhill very rapidly. *8th day:* fits began and continued till she died on evening of *9th day*.

CASE 2.—A girl, aged 10 months, received K60 on March 18, 1937; 71 days later, on May 28, refused 6 PM feed. *2nd day:* vomited after morning feed; irritable; objected to being moved about; slight rash between legs. *3rd day:* rash became general. *4th day:* rash faded; refused feeds; stool semi-solid; child pale; conjunctivæ slightly yellow; passed large white fatty stool. *6th day:* coffee-ground vomit first seen by doctor in afternoon; definitely jaundiced; temperature and pulse normal; another large coffee-ground vomit and at 5.45 PM died suddenly (June 3).

CASE 3.—A girl, aged 7 years, received 5 c.cm. of K60 on Feb. 26, 1937; 62 days later, on April 29, vomited after breakfast but was able to travel 120 miles. Well throughout day but vomited several times in evening. *2nd day:* sleepy and off colour; constipated; no abnormal physical signs. *3rd day:* poor appetite; listless; no fever; no abnormal signs. At 1 PM became restless and began screaming; generalised abdominal pain, so enema given which resulted in flatus only; not thought to be ill; chastised by mother for screaming which continued throughout night. Seen again by doctor during night; temperature and pulse normal but very restless; examinations, possible only in calmer intervals, negative; vomiting frequent. *4th day:* small coffee-ground vomit at 8 AM, becoming profuse later in the day; first noticed to be slightly jaundiced. Child found lying on floor; when attempt made to pick her up she struggled violently and crawled under furniture. Heroin, gr. 1/4, given at noon and child became quieter, but at 4.30 PM she was restless and screaming and was noticed to be rigid. At 6 PM was unconscious; slightly jaundiced; various bruises from her struggles. Temperature 100° F., pulse-rate 80. Tongue and throat dry and red. Pupils small and reacted only slightly to light; fundi and eardrums normal; well-marked divergent squint with independent movement of eyes. General flaccidity apart from jaw and neck; abdominal reflexes absent, plantar responses strongly extensor, other reflexes brisk; no Kernig sign. Short systolic murmur at base of heart, otherwise heart and lungs normal. BP 130/70 mm. Hg. Liver edge firm, palpable 1 in. below costal margin; abdominal movements normal, peristalsis heard. Urine contained bile and trace of protein. Cerebrospinal fluid normal. At 7 PM several coffee-ground vomits and tetany. At 9 PM condition worse with spasms of generalised rigidity, cyanosis, Cheyne-Stokes breathing and bad pulse; coffee-ground vomits continued. Died on May 3, *5th day* of disease. Autopsy obtained.

CASE 4.—A boy, aged 4½ years, brother of case 3, received 5 c.cm. of K60 on Feb. 26, 1937; 63 days later, on April 30, developed malaise, vomiting and constipation; trace of tenderness in right loin. *2nd day:* did not appear to be ill; temperature normal; urine contained trace of protein but no bile. After 2 PM, except for drowsy intervals, restlessness and screaming continued throughout night, during which child was delirious and twice fell out of bed. *3rd day:* better and sitting up, but at 1 PM produced a coffee-ground vomit and later became drowsy. By 6.30 PM looked ill; slightly jaundiced; on any attempt at examination screamed and struggled violently. Bruises on body from struggles during night; optic fundi normal; eardrums a little injected inferiorly; tongue dry and red. Examination difficult. Extensor plantar responses were the only abnormal sign found except for a firm liver palpable 1 in. below costal margin. Lumbar puncture impossible on account of struggles but child drowsy throughout night. *4th day:* quiet; temperature normal; took fluids well and seemed better. At noon coffee-ground vomiting became continuous and at 6 PM tetany appeared; temperature 99·6° F. At 6.30 PM became worse; temperature 100·6° F., pulse-rate 145. At 8 PM transfused with 100 c.cm. of father's blood (both group A). At 9 PM was a little better with pulse-rate 90 but vomiting continued and became more bloody. Died at 11.40 PM (May 2).

Records of 5 autopsies are available, but, with two exceptions, are sketchy and incomplete. The findings recorded are set out in table II.

TABLE II—AUTOPSY FINDINGS IN CASES OF MEASLES SERUM HEPATITIS

		K60	K488	Total
No. of autopsies		4	1	5
Skin:	Bruises	1	..	1
	Jaundice	1	..	1
Intestines:	Extreme catarrh	1	..	1*
	Superficial necrosis	1	..	1
Liver:	Subacute atrophy	1	..	1
	Fatty degeneration	1	1	2
	Gross necrosis	3	..	3
Heart:	Fatty degeneration	1	..	1
	Necrosis	1	..	1
Kidneys:	Fatty degeneration, necrosis	3	..	3
Hæmorrhages:	Blood in stomach	2	1	3
	into viscera	1	1	2
	into serous sacs	1	1	2
	into brain	1	..	1

Histology.—Blocks from 4 cases showed widespread atrophy of the liver cells; few of these appeared normal and the majority showed extensive vacuolation with "foamy" cell body and degenerative changes in the nuclei. Elsewhere numerous liver cells were completely necrotic. The records do not mention the orientation of the damage in the liver and it is not clear whether the necrosis was mainly central, peripheral or uniformly diffuse. There is nothing characteristic about the descriptions of microscopic lesions in other organs.

LABORATORY INVESTIGATIONS

For the most part the available reports relate to the acute stage of the illness. Table III shows the available white counts.

TABLE III—WHITE CELL COUNTS IN CASES OF MEASLES SERUM HEPATITIS

Case	Day after onset of jaundice	Total whites	Percentages					
			Polymorphs	Lymphocytes	Monocytes	Large hyaline	Myelocytes	Eosinophils
A	38	..	52	37	..	4	4	3
	42	..	52	38	..	3	4	3
	47	..	65	30	..	3	..	2
B	..	..	58	38	..	1	..	2
C	15	Apparent leucocytosis	79	19	..	2	..	..
	35		48	51	..	0	..	1
D	18	Apparent leucocytosis	82	16	..	2	..	..
	..		53	43	..	1·5	..	1·5
E	..	4950	54	21	25	..	..	1
F	..	6400	52	38	9	..	..	1
G*	4†	14,200	80	12	7	..	..	1
H	17		25	66	2	..	..	7
I	..	5330	29	64	3	..	..	2‡

† Three hours after transfusion and one hour before death.
* Fatal case. ‡ One mast cell per cent.

Two red-cell counts are recorded, both during the acute stage, in cases F and G of table III. The second case died soon after the count and had been bleeding. Case F: reds 4,050,000; Hb. 80%; CI 1. Case G: reds 4,430,000; Hb. 70%; CI 0·8.

Bacteriological findings were negative in the following investigations (K60 cases only). Animal inoculations of blood, urine or post-mortem fluid, including tests for leptospirosis, 7 cases. Microscopy of tissues and/or culture, 5 cases. Cerebrospinal fluid, cytology, chemistry and culture, 1 case. Widal reaction, several cases.

Urinary bilirubin (Fouchet's test) was negative in 4 cases six months after onset.

Findings were positive in the following investigations.

Van den Bergh, 6 cases (during acute stage unless otherwise stated).

Direct positive (26 units in 1 case)	4 positive
Delayed direct	1 "
Indirect positive 0·4 unit	1 "
2·0 units (10 months after onset)	1 "

In the last case serum bilirubin (Fouchet) was weakly positive 10 months after onset and the serum showed no immunity to yellow fever.

Urinary urobilin was determined in 4 cases six months after onset and was abnormal in 2, suggesting excessive hæmolysis or persistent liver damage.

Lævulose-tolerance test was abnormal twelve months after onset in 1 case (50 g. lævulose by mouth).

Fasting blood	100 g. per 100 c.cm.
1 hour	133 " " "
2 hours	111 " " "

INVESTIGATIONS ON THE SUSPECTED SERUM

No record of any similar incident could be found in the published work and opportunity was taken to consult such persons * as it was thought would be able to throw light on the matter. The problem was discussed from every angle which may have been even remotely concerned, but no conclusion was reached as to the mechanism of the disease, although the majority opinion attributed it directly to the "measles" serum. Since the case against K60 was most firmly established the unused residue of this batch was submitted to tests unfortunately limited by the small volume of serum available.

K60 was found to be sterile and to contain the proper quantity of antiseptic: 0·5% of an equal mixture of phenol and ether.

1 c.cm. was injected intracardially into each of 10 guineapigs. All survived the injection; 4 were killed on the second day and all organs found healthy both macroscopically and microscopically; the remaining 6 were killed on the 100th day and all organs were healthy.

A sample of the serum was ashed and analysed spectroscopically. As, Ba, Cd, Co, Mn, Ni, Ti, Tl and V were entirely absent. Exceedingly minute traces of Bi, Cr, Pb, Sb, Sn and Zn were detected, the evidence for antimony depending on a single very feeble line. There was nothing to suggest the presence of a hepatotoxic inorganic element.

Microscopic and dark-ground investigations failed to reveal any bodies which could be characteristically differentiated from the myriads of particles of all shapes and sizes seen.

The biophysical properties of K60 were compared with those of a control batch. Osmotic and refraction measurements on clarified sera showed the quotient "osmotic pressure/refraction increment" to be the same on the two samples. The value was less than that given by normal serum but not small enough to indicate gross disintegration of proteins. Ultracentrifuge fractionation revealed close similarity in the molecular composition of the two sera. In addition to the albumin boundary, three globulin components were present in both. The only difference between K60 and the control was a much more bulky deposit upon slow speed centrifugation of the K60. Since the serum was candled before bottling this deposit was either precipitated out of the serum, or foreign matter, living or dead, introduced since candling.

Donors were interrogated, particularly with regard to a past personal or family history of jaundice, asthma, urticaria or other allergic upset. The results were negative but serum was taken from two of the donors who had had some apparently unrelated illness years previously. These sera were used in agglutinations, precipitation and other serological tests to which K60 was also submitted. The donors' red cells were also investigated serologically. The blood of guineapigs injected intracardially with K60 was included in these tests, the results of which were not helpful. There is no record of any attempt to perform serological or sensitivity tests using K60 against those who survived jaundice.

DISCUSSION

In no single case of hepatitis could it be proved that natural causes were not operative, but on the epidemiological evidence the majority of the investigators concluded that the causal factor resided in K60 and possibly in K488. Conversely it was difficult to suppose a contributory abnormality in the recipients because of the high percentage of the inoculated who suffered from the disease. The causal abnormality may have been introduced during the handling of the serum—e.g., a non-specific delayed action poison; or a known or unknown virus with long incubation period. It may have been derived from one of the contributors—e.g., a virus which

* Representatives of National Institute of Medical Research, London School of Hygiene and Tropical Medicine, Lister Institute of Preventive Medicine, Wellcome Physiological Research Laboratories, London County Council, Metropolitan Police Laboratory and General Register Office, and the Directors of Hygiene to the Services were consulted, as were also a number of clinicians.

could withstand carbolic and ether and has a long incubation period; or a mysterious antigen occurring naturally in one of the donors or produced by the interaction of several sera or by denaturation by antiseptics, or a sensitising serum from a sensitive donor, only 0·2 c.cm. of which would be received by each of the recipients of K60.

Sections of liver from 4 cases were specially stained by methods designed to demonstrate inclusion bodies. In 2, cytoplasmic inclusions were found which stained with acid dyes. No intranuclear inclusions were detected and the opinion was that cytoplasmic inclusions in degenerated liver cells could not be used as evidence of virus disorder since they have been found in 30% of livers at autopsy irrespective of cause of death. They have also been observed in the livers of normal monkeys, ferrets and guineapigs (Pappenheimer and Hawthorn 1936). Certain appearances suggested that some of the acidophil inclusions seen in the K60 cases arose from degenerated nuclei; the numbers found were small and quite disproportionate to the very extensive liver changes. No other evidence of virus disorder was detected histologically.

It was thought that the long "incubation period" (on the assumption that the causal factor was introduced into the diseased persons at the time of injection) was an argument against a virus infection; it was an equally strong point against any known "allergic" explanation. Since the investigations further information has become available concerning the "incubation period." Both the date of administration of serum and of onset of jaundice are known in 48 cases, as follows.

Batch	Cases	Incubation periods		Deaths	
		Range	Median	No.	Median day
K60	37	16–114th day	71	7	75
K488	11	78–161st day	123	1	134

The difference in array may have some significance and will be discussed later. K60 was prepared in April, 1936; K488 on Feb. 12, 1937. It was clear that numerous batches of serum produced in the same laboratory even at about the same time were not followed by jaundice. It is interesting that inquiry has failed to bring to light any evidence that jaundice had followed measles serum from other laboratories in this country or has come to notice in the USA or other countries represented at the International Health Division. For more than ten years the London County Council has used, as a routine, measles convalescent and adult serum for prophylaxis and attenuation in its hospitals; 366 litres obtained from over 3000 donors and processed in the LCC laboratories has been employed for this purpose and the majority of 36,000 recipients have been followed up after an interval of two months or more; no case of jaundice has been detected among them. The American serum institutes distribute homologous serum for various purposes on a very large scale. There is no record of jaundice having resulted from these practices, and generally speaking there is no evidence that measles attenuation with adult or convalescent serum is fraught with especial danger. K60 was obtained from measles convalescents and K488 was adult serum.

Transfusion Hepatitis

With the preceding summary in mind the incident at the EMS hospital can be discussed more effectively and the histories of two of the cases will be summarised.

CASE 5.—A toolmaker, aged 51, had suffered from intermittent claudication for 4–5 years. In December, 1940, he was buried in debris and sustained a Pott's fracture which was treated in plaster applied on Dec. 6. Plaster sores persisted, an ulcer 1½ in. in diameter developed and he was transferred to a medical ward (MG 1) for serum transfusion and remained there. He received 800 c.cm. of dried, reconstituted serum on six occasions (Jan. 29, 1941; Feb. 4, 11, 18, 25 and March 17, 1942). The batch and bottle numbers of the serum administered were not recorded except in the case of the last transfusion, and the origin of $\frac{5}{6}$ths of the total of 4·8 litres used cannot be identified. All the serum was, however, processed at one and the same laboratory.

On May 24, 1942, 68 days after the last transfusion, a scarlatiniform punctate erythema appeared on the chest, abdomen and legs. The temperature rose steadily day by day until on the 7th day it reached a peak of 103·2° F.; thereafter it resolved by lysis, becoming normal 13 days after the appearance of the rash. Jaundice was noticed on May 26 or 27, when the liver was enlarged three finger-breadths and was tender. The stools were pale but not putty coloured. The spleen was not felt and there was neither vomiting nor bleeding. By June 19 the urine was free from bile, the liver not palpable and the jaundice almost gone. The plaster ulcer healed dramatically during the course of the jaundice.

CASE 6.—A publican, aged 58, was well until November, 1940, when he developed gangrene of the foot complicating thromboangeitis obliterans. He was admitted to hospital on Dec. 14, 1940. His foot was removed, and apart from two periods of leave in 1941 he remained in hospital. He received eight serum transfusions of 800 c.cm. each: four in ward MG 2 on Sept. 15 and 29 and Oct. 7 and 17, 1941, and four in ward MD on Feb. 12, March 1 and 20, and April 1, 1942, the second period of leave, at Christmas 1941, intervening between the two series of transfusions. He was transferred to ward MG 1 on May 6, 1942. On the morning of June 27, 1942, he answered his nurse's inquiry with the words "In the pink" and thought she was joking when she replied "You look yellow." Bile-pigments were present in the urine on this day, but apart from mild depression and drowsiness for two days beginning on June 29, and a rise in temperature to 99·0° F. there was no constitutional disturbance whatever.

At the time they developed icterus these men occupied beds fifteen feet apart in a ward containing 19 patients, of whom they were the only two who had received serum. Thirty-two days intervened between the dates of onset of jaundice in the two cases, and this interval conforms with the incubation period of epidemic hepatitis. No member of the staff of the hospital and no other patient in the ward had jaundice during material periods.

Although 5 of the remaining 6 cases of transfusion jaundice were transfused in other wards and 2 subsequently developed jaundice while still in this hospital, there were no circumstances suggesting previous contact with epidemic (catarrhal) jaundice. The evidence suggests that serum transfusion per se has caused hepatitis indistinguishable from that following convalescent measles serum, convalescent mumps serum and yellow fever vaccine containing human serum.

The appearance of this phenomenon was anticipated at the Ministry of Health where information had previously been received of another grave case of jaundice following whole blood and plasma transfusion, and on Aug. 13, 1942, a meeting of the principal blood-transfusion officers was called to inquire, inter alia, whether this was an isolated case or whether transfusion was more frequently followed by hepatitis. It transpired that not until Aug. 12 did the cases in the EMS hospital come to the notice of the transfusion officers. Since then the condition has been observed at three other hospitals and the total of known cases following transfusion is now 12. It must, however, be remembered that no systematic follow-up of transfused patients has been attempted, and that, since an association between transfusion and late jaundice is unlikely to be recognised spontaneously, it is not to be expected that such remote sequelæ would be brought to the notice of the blood-transfusion officers. For this reason it cannot be assumed that whole blood is innocent or that plasma is likely to be less icterogenic than serum.

Clinical Picture of Homologous Serum Jaundice

The description of jaundice following measles serum is based mainly on records of a few severe cases. The attacks following mumps convalescent plasma and yellow fever vaccine were for the most part less dramatic.

The cardinal sign of the condition has been jaundice but it is probable that the disorder occurs without the appearance of jaundice; thus, one child of a number receiving an otherwise implicated measles serum died of "meningismus" some twelve weeks later. The intensity of the jaundice and of liver damage has varied. Measles convalescent serum gave rise to fulminating hepatic necrosis and widespread pathological changes in other organs. Mumps convalescent serum produced relatively mild disease. In Brazil yellow fever vaccine

TABLE IV—SIGNS AND SYMPTOMS IN 48 CASES OF JAUNDICE FOLLOWING MUMP CONVALESCENT SERUM

—	Severity of disease			Total no. of times symptoms mentioned	Per cent. incidence of symptoms
	Mild	Moderate	Severe		
Cases (total 48) ..	38	9	1		
Symptoms recorded					
Skin rashes	17	3	0	20	41·7
Anorexia	33	7	1	41	85·4
Abdominal pain ..	10	2	0	12	25·0
Indigestion	26	5	0	31	64·6
Change of bowel habits	13	2	0	15	31·2
Fatigue or sleepiness	25	6	1	32	66·7
Dark urine ..	37	9	1	47	97·9
Stiff joints	9	2	1	12	25·0
Headache	11	0	1	12	25·0

—	No. of cases in which observation recorded	No. of cases in which sign present	Per cent. appearance of signs
Signs recorded			
Jaundice : slight	48	17	35·4
moderate		22	46·8
severe		9	18·7
			100 %
Rash	47	9	19·1
Conjunctivitis ..	41	27	65·9
Petechiæ, hæmorrhages &c.	48	7	14·6
Liver enlarged ..	48	32	66·7
Liver tender	47	21	44·7
Spleen palpable ..	48	18	37·5
Spleen tender ..	47	9	19·1
Lymphadenopathy ..	47	8	17·0
Urine : bile	45	45	100%
albumin ..	42	22	52·4
casts	47	8	17·0

caused a significantly greater proportion of jaundice in the age-groups above 20 years.

No sign differentiating this condition from hepatitis due to other causes has been recognised, but most of the studies have been retrospective. The association between jaundice and homologous serum has been seldom suspected until the patient was either dead or recovered, and critical clinical observations have been reported in rare instances only. These reports suggest that differentiation from epidemic hepatitis should be possible and that erythema multiforme, stiff joints and splenic enlargement may in time be recognised as distinguishing points.

The most complete clinical survey so far available comes from the ARC Harvard Unit Hospital, where 48 men who had received mumps convalescent serum were subsequently treated for jaundice (table IV). The clinical severity of this series was classified as 79·2% mild, 18·8% moderate and 2·0% severe, and the severity was not necessarily proportionate to the degree of jaundice.

In 41·7% of the histories mention is made of the appearance of polymorphic rashes distinct from the petechial, purpuric and xanthomatous rashes usually associated with grave and persistent jaundice. Although the greatest incidence of rashes so far recorded occurred after mumps convalescent serum the notes of 6 of 34 measles serum cases also mention "urticarial" rashes. The history of two of these patients was as follows.

CASE 7.—A boy, aged 5 years, received 4·5 c.cm. of K60 on June 1, 1937; 18 days later, on June 19, developed swelling of lips on left side and of joints. June 21, urticarial rash; temperature 101° F. June 24, temperature normal, rash gone. Aug. 12 (73 days after serum), fever and vomiting; appeared bright for about two days. Aug. 21, convulsions, delirium and coma; vomited terminally coffee ground; fever up to 103° F.; mild jaundice deepening after death.

CASE 8.—A girl, aged 8 years, received 4·5 c.cm. of K60 on April 1, 1937; 79 days later, on June 18, vomited. *3rd day:* vomiting. *5th day:* jaundice which deepened steadily until 19th day. *15–19th day:* drowsiness marked with periods of delirium; fever variable, up to 100° F. *26th day:* urticaria, rigor and temperature up to 100·2 F°. This was the third attack of urticaria accompanied by restlessness and fever during the course of disease. Rash was patchy and erythematous, fading in 3–6 hours. No history since 26th day. Child recovered.

The polymorphic rashes usually preceded jaundice by a few days only, but this period was in some cases extended to more than a month. On the other hand, there was nothing to suggest a comparison between these rashes and the urticaria of heterologous serum fever which usually occurs during the second week after injection. Although the rashes were polymorphic they should probably be grouped into one category as erythema multiforme. The "urticarial" types were not migratory and evanescent but tended to be fixed and to leave staining; they were commonly papular, pruritic and centrifugally disposed. Erythema circinata was seen and also a punctate erythema in discrete patches. In other cases the rash appeared on the abdomen and suggested pityriasis rosea; in others again it resembled psoriasis and became scaly. In one patient a hæmorrhagic rash and other signs led to a clinical diagnosis of meningococcal septicæmia, but he subsequently developed jaundice.

Another characteristic prodromal sign was stiffness in the joints of the extremities, particularly in the mornings. Pre-icteric pruritus was inconstant but occurred and a variable degree of fever was present. Anorexia and nausea appeared early with a sensation of heaviness in the epigastrium; this aching was exaggerated by walking or running and the patients said they thought they could feel their abdominal viscera bouncing. Vomiting was rare. Dark urine appeared three or four days after these prodromata and subsequently icterus developed gradually.

LATENT PERIOD

A feature present in all instances has been the long interval between the injection of human blood products and the appearance of the jaundice. The "incubation" period is most commonly 60–90 days (table V).

TABLE V—APPARENT INCUBATION PERIODS IN HOMOLOGOUS SERUM JAUNDICE

—	No. of cases of jaundice	Incubation period (weeks)		
		Array	Med.	Av.
Humanised lymph ..	191	(Several weeks to 2 months)		
Measles convalescent serum (K60) ..	41	2–16	10	..
Measles adult serum (K483) ..	11	11–23	17	..
Yellow fever vaccine—				
(*a*) Brazil Lot no. 467	81	16–21	16–21	..
Lot no. 489	736	2–68	..	17·8
Lot no. 490	150	2–80	..	20·4
(*b*) American troops in U.K. Lot no. 338	29	12–32	21	..
Lot no. 351	53	8–24	15	..
Lot no. 368	169	5–28	13	..
Mumps convalescent serum	62	5–19	11	..
Serum transfusion * ..	5	10–12 (min.)	11	..
		14–41 (max.)	17	..

* Peripheral vascular disease.

Although there is a wide array in most of these examples the curves show peaks about the median. The peaks for different batches do not coincide, suggesting considerable differences in the latent periods of different batches of the same inoculum. This point is worthy of investigation.

ANALOGOUS CONDITIONS IN HORSES

Disasters suggestive of the incidents described in this paper have been observed in horses. In England, 15 c.cm. of lamb dysentery horse serum prepared early in 1935 was given subcutaneously to each of 617 horses in 9 areas. An equally large group of untreated animals was observed as control. Although the serum had given no trouble when used in lambs in the same year, about 6 weeks (average 53 days) after injection some of the horses developed urticarial swelling of the nostrils and face followed by a long period of local desquamation. A proportion of the affected animals became dangerous to handle, attempted to savage their attendants and plunged wildly about before developing a staggering gait and eventually complete paralysis. Most of the affected animals showed well-marked icterus of the visible mucous membranes. In 30% (182) of the inoculated animals the disease was mild and might have been regarded as clover

sickness, 3 cases of which occurred among the control group. In 7·6% (47 of 617 inoculated) the disease was fatal and might have been diagnosed as "mad staggers," no case of which occurred among the control group. Yellow atrophy of the liver was a prominent feature at autopsy (Gordon 1935).

In Montana, 5193 horses were treated with either 2 c.cm. of 20% suspension of guineapig brain infected with equine encephalomyelitis in 50 c.cm. of horse serum used as a diluent, or with serum alone. Between the 32nd and 89th day after injection 89 animals became ill and 79 died "on their feet." Symptoms were excitement, muscular tremors, impaired vision and sweating. Mucous membranes were somewhat icteric. Some of the 89 had received serum alone. Later similar symptoms appeared in unimmunised animals, but out of a group of 861 horses 2 only died (Marsh 1937).

The first report of "mad staggers" apparently following the injection of homologous serum into horses came from South Africa. Staggers, jaundice and acute necrosis of the liver appeared 62–78 days after inoculation against horse sickness. It was later found that staggers" had occurred in 4 of 160 non-immunised horses in the same district (Theiler 1919).

In Norway, anti-anthrax serum was produced from horses and cows, and either homologous or heterologous serum was injected into both. Acute or subacute necrosis of the liver occurred in the horses receiving homologous serum after an interval ranging from 8 to 97 days (50–60 days in the majority). In this group 4% (101) were affected and 50 died. The cows treated with either serum and the horses treated with heterologous serum were not affected (Stagsvold 1938).

Comment

The examples of homologous serum jaundice collected in this paper make it clear that the subject is one of major importance. Our understanding of the mechanism has not advanced since 1937 when measles serum jaundice was first described. One conclusion is now, however, evident: any doubt as to the reality of the association is removed by the frequency with which hepatitis has followed the injection of human blood products. The probability that further cases will occur, particularly after transfusion, must be faced.

Although ætiological studies are proceeding both in England and America it is unlikely that the problem will be easily solved or that a radical method for preventing the phenomenon will readily be found. Since there can be no question of withholding transfusion in emergency, prevention will for the time being depend on the identification and withdrawal of icterogenic batches of serum and plasma. Timely identification may be possible only under exceptional circumstances; it will depend on the care with which batch numbers are recorded at the time of transfusion, and on the speedy notification by practitioners to transfusion officers of cases of jaundice following, after a long interval, the injection of blood products.

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BIBLIOGRAPHY

Bulmer, G. (1923) *J. Amer. med. Ass.* 81, 353.
Chief Medical Officer (1937) On the State of the Public Health, London, p. 39; (1938) *Ibid*, p. 21.
Editorials (1942) *J. Amer. med. Ass.* 119, 1110; 120, 53; *Lancet*, ii, 515.
Findlay, G. C. M. and MacCallum, F. O. (1937) *Trans. R. Soc. trop. Med. Hyg.* 31, 297; (1939) *Ibid*, 32, 575.
Fox, J. P., Manso, C., Penna, H. A. and Para, M. (1942) *Amer. J. Hyg.* 36, 68.
Gordon, W. S. (1935). Quoted by Findlay, C. M. and McCallum, F. O. (1938) *Proc. R. Soc. Med.* 31, 799.
Hayward, G. W. (1942) *Brit. med. J.* i, 285.
— and Jordan, A. (1942) *Ibid*, i, 462.
Hirschberger, C. (1936) *Acta paediat.* 18, 482.
Jervis, J. J. (1939) Annual report MOH, Leeds.
Lurman (1885) *Berl. klin. Wschr.* 22, 20.
Marsh, H. (1937) *J. Army vet. med. Ass.* 44, 88.
Pappenheimer and Hawthorne (1936) *Amer. J. Path.* 17, 625.
Propert, S. A. (1942) *Brit. med. J.* i, 197.
Spec. Rep. Ser. med. Res. Coun. Lond. 1938, No. 227.
Stagsvold (1938) *Norsk. vet Tiddskr.* 50, 69.
Symmers, D. (1920) *J. Amer. med. Ass.* 74, 1153.
Theiler, A. (1919) *Rep. vet. Res. S. Afr.* 5, 7.