Section of Epidemiology and State Medicine

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[*March* 24, 1939]

The Epidemiology of Jaundice

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THERE are two forms of infective jaundice seen in this country, Weil's disease and common infective jaundice. Jaundice associated with other diseases, such as pneumonia, typhoid, and paratyphoid infections, does not come within the scope of this discussion.

WEIL'S DISEASE

I shall not say much about this disease. Excellent accounts of the epidemiology and references to the literature are given by Davidson and others (1934 and 1936) and by Alston and Brown (1937). Weil defined the entity in 1886 and Inada and Ido discovered the causal organism, the *Leptospira icterohæmorrhagiæ*, in 1915. Recently the disease has been recognized in this country, but is still relatively uncommon. Alston and Brown (1937) were able to refer to 142 cases collected from the literature and other sources from July 1933 to February 1937. Since then other accounts have appeared from Davidson (1938), concerning fish-workers in Aberdeen; Swan and McKeon (1938), coal-miners in N.E. England; Stuart (1938), Glasgow tripe-workers; Naftalin (1938), a case following violent immersion in a canal; Robertson (1938), four cases from the same stream in the south of England; Stuart (1939), Glasgow sewer-workers; and Rees (1939), six cases in miners from the South Wales coalfield.

Even up to the present time under 200 cases have been reported in Great Britain, although there is evidence of past infection in more.

Rats are almost always the direct or indirect source of infection in man. The excreted leptospira can remain alive in water, particularly in slime, but die quickly in an acid medium, in strong sunlight, or in salt water. They enter the body either through cuts and scratches on the sodden skin and also, some think, through the upper respiratory tract or even the conjunctivæ. These requirements narrow down the incidence of the disease to certain particular occupations of which sewer-workers, fish-workers, coal-miners, and bathers (particularly violent bathers), head the list.

The clinical picture and laboratory methods of diagnosis are now well known. The incubation period is usually seven to thirteen days. The mortality is in the region of 15%. Early diagnosis is important as it is then that antiserum is of greatest value. Not only are there the classical cases with sudden onset, headache, severe muscle pains, nausea and vomiting, prostration and fever, watery conjunctival suffusion and albuminuria followed in four to seven days by jaundice, but there are, as Davidson (1938) remarks, mild infections with fever and malaise but without jaundice. If, combined with these symptoms, there is a history of suitable occupation and circumstance, the disease should at once be suspected. Although uncommon, cases are more frequent than is supposed. Dr. Wolstencroft (1939), who has been

interested in the disease, tells me that he has seen three in three years in one small country town ; the first in a canal labourer (published 1935), the second in a gravel-pit worker, and the third in a worker in a rat-infested paper-mill on the banks of the canal.

In spite of endeavour, it seems unlikely that the particular occupational sites will be rid of rats and prevention of the disease will largely depend on prophylactic active immunization.

Common Infective Jaundice

Incidence.—Common infective jaundice (" catarrhal jaundice " ; " common infective hepatic jaundice ") is a frequent and widespread disorder in this country. The causative agent is unknown. It appears in epidemics, but cases which are apparently sporadic are also seen. As the clinical course is usually mild and the disorder is not generally notifiable, accounts of it are relatively few. Nevertheless, the number of cases recorded in different outbreaks in various localities is sufficient to form a fair sample of the whole. The following is a list of reports of outbreaks in this country which have appeared in the last twelve years. The list includes certain important unpublished epidemics, and I am greatly indebted to Dr. Brincker, Dr. Alison Glover, and Dr. J. L. Newman, for showing me the accounts of these and allowing me to quote from them.

Reports of Outbreaks of Epidemic Infective Jaundice in England : 1926–1939

Authors	Date of report	Place	No. of cases
Martland and Winner	1939	London	4
Newman	1939	Sussex (South)	130+
The School Epidemics Committee	1938	Different localities. 77 small outbreaks in various schools	158
Brincker	1938	London (L.C.C. schools, &c.)	193
Simpson (not yet published)	1938	Devon (Torquay)	5
Sergeant	1937	Durham (Gateshead)	49
Barber	1937	Derbyshire	?
Lisney	1937	Leicestershire	40
Pickles	1936	Yorkshire (Wensleydale)	19
Bates	1936	Gloucestershire (Stoke Park)	65
Ramage	1935	Lincolnshire (Holland)	26
Frazer	1935	Staffordshire (Newhall)	25
Beauchamp	1934	?	3
Bashford	1934	London (G.P.O.)	48
Montford	1934	Leicestershire (Castle Donington)	45
Booth and Martyn	1933	Lincolnshire (Holland)	13
Findlay, Dunlop and Brown	1931	Surrey	190
Glover and Wilson	1931	A country town	106+
Pickles	1930	Yorkshire (Wensleydale)	250
Butterworth and Brothwood	1930	Lancashire	25
Brown and Gardner	1927	Oxford (approx.)	*200
Morgan and Brown	1927	Midlands	200
Booth and Okell	1927	Surrey	106
			1900+

* Personal communication.

It will be seen that the outbreaks are widely scattered over the country and have taken place at different times. Yet, wherever the syndrome is seen, it has the same essential clinical and epidemiological features, suggesting strongly that it is one disease process and probably that it has one specific cause.

The disease is common and infective, and for these reasons I have called it common infective jaundice. This does not commit us to a pathology the exact nature of which is still sometimes disputed.

It is often said that the disease is one of rural areas. I doubt the truth of this. Plenty of cases are seen in London hospitals and in London schools (Brincker, 1939).

I think the idea of rural incidence has arisen simply because the disease is more easily seen and traced in small country villages and towns and therefore more often remarked and reported, especially as the incubation period is long and the infectivity often low.

Outbreaks usually start between the months of August and March, and may continue throughout the year, although the incidence is less in the summer months.

Epidemics involve communities of people who are in close contact with each other, as in schools and families, particularly in children of the school ages of 6 to 10. Children of pre-school age are not exempt. Adults, particularly young adults, are by no means immune. For example Bashford (1934) describes an outbreak of 48 cases in a section of the London General Post Office in which all the patients were adults, mostly young. In many of the general epidemics about a fifth of the patients were adults. Pickles (1930) suggests that the disease attacks all ages indiscriminately and that it is seen mainly among school children because the school provides the opportunity for infection. From the available data, however, it does seem that adults have more immunity than children, although the symptoms tend to be more severe. The sexes are equally affected.

Clinical features.—Common infective jaundice is milder than Weil's disease and clinically distinct. Its mildness in this country is characteristic. It should be remembered, however, that a severe case of the milder disease may possibly simulate a mild case of the more severe, and if there is the slightest doubt of the nature of an outbreak, Weil's disease should be excluded as quickly as possible.

The clinical features are remarkably constant, although the nature of the disease is usually not apparent until bile has appeared in the urine, or jaundice is seen.

Frequently, there is a prodromal stage of indefinite malaise from one to seven days before the onset of acute illness. In one epidemic (Glover, 1930) there was a prodromal period of lassitude lasting from three to four weeks. The onset starts acutely, usually with fever. The temperature may rise as high as 103° F., but falls again within the next day or two. This initial fever is seldom remarked, as the temperature is not often taken at the onset. The patient is usually described as having a " chill " or " huddled in front of the fire " (Newman, 1939), but there are no rigors. Headache is frequent for the first two or three days and occasional drowsiness. Loss of appetite is complete. Nausea is common. Vomiting, often severe and intractable, is characteristic though not invariable from the onset. Abdominal pain or discomfort is common, typically in the epigastrium and less often in the right upper quadrant of the abdomen. Jaundice appears in anything from 0 to 12 days from the acute onset, and is seen first in the conjunctivæ and then in the face and neck. In mild cases it lasts only a few days, but in the more severe it may persist for three weeks or more. The appearance of jaundice usually coincides with the beginning of convalescence and the end of the initial symptoms. On examination, in the early stages, there is often epigastric tenderness and, later, sometimes tenderness over the region of the gall-bladder or the enlarged liver. I have seen a case in an adult in which severe vomiting with epigastric tenderness had persisted for nine days ; then for the first time there was localized tenderness, worse on inspiration, just below the tip of the right ninth costal cartilage ; two days later there was jaundice. During the stage of jaundice the liver is frequently enlarged. My impression is that the longer the jaundice lasts the greater is the enlargement. In adults it is not unusual to find the liver extending down as much as three fingerbreadths below the right costal margin, although this is seldom found in children in whom the disease is shorter. In some epidemics the gall-bladder is said to have been palpable ; personally I have never been able to elicit this sign. The spleen is occasionally palpable. The urine contains bile pigments, and when this can be dated the urine is dark one or two days before the jaundice appears. This valuable sign is stressed by Dr. Newman (1939). I should like at this point to refer to a bedside test for latent jaundice worked out by Dr. Brodribb and myself (1936) which was first described by Klein (1931).

The equivalent of 0·1 mgm. of histamine in a one minim solution is injected intradermally into an area of skin devoid of sunburn or freckles. After ten minutes a wheal appears surrounded by a red zone. In good daylight, a piece of glass is pressed over the wheal and the colour of the centre compared with the colour of the skin outside the red zone. If there is a concentration of bile in the blood-stream corresponding to one unit of van den Bergh (0·5 mgm.% serum bilirubin) or more the centre of the wheal is distinctly yellow.

This is a useful bedside test for latent jaundice as one cannot recognize commencing jaundice with the naked eye until the bilirubin in the blood-stream has reached a concentration of nearly 4 units of van den Bergh (2 mgm.% serum bilirubin).

Bates (1936) draws attention to the presence of acetone in the urine when looked for early in the disease. A number of his cases had no vomiting, fever, or starvation, and he thinks it is due to a maladjustment between the fat and carbohydrate metabolism caused by hepatic damage. Albumin is occasionally seen in the urine, particularly in the more severe cases. The bowels may be constipated or loose with offensive motions. The stools are usually clay-coloured at some period of the illness, but frequently contain bile when jaundice is established. Blood: in contradistinction to Weil's disease there is no leucocytosis and often a leucopenia. There is a relative or absolute increase in lymphocytes or monocytes or both. Other symptoms: Probably because of the short duration of the jaundice itching is uncommon. Epistaxis is rare. Conjunctivitis is seldom seen. Urticaria is occasionally described. Peeling has been observed in a few cases. Sore throat is recorded in only a few epidemics. It was present in the early cases of the large school epidemic described by Glover and Wilson (1931) and in the three cases described by Beauchamp (1934). In the latter epidemic, however, although the throats were negative to K.L.B., there was a concurrent epidemic of diphtheria. I believe that sore throats are incidental and not really part of the clinical picture of the disease.

Convalescence.—Lasts from one to three weeks.

Severity.—The disease in this country is usually mild, especially among children. Morgan and Brown (1937) refer to two severe cases in an epidemic of 200. One of these died, and I will refer to the post-mortem findings later. My impression is that the disease is of longer duration and greater severity in adults than in children. Further, I am not convinced that the disease is always as mild as is supposed, but I will discuss this point later when speaking of subacute necrosis of the liver.

Recurrence.—Occasionally the disease recurs. Findlay, Dunlop and Brown (1931) refer to a case in which jaundice recurred two months after the primary attack, and Bates (1936) a boy of $8\frac{1}{2}$ who had a second attack of jaundice thirty-four days after bile had disappeared from the urine; the second attack was more severe than the first. I know of a London surgeon who had the disease in childhood at least three times.

Complications.—Apart from the possibility of subacute necrosis of the liver, complications are very rare. Glover (1933) refers to one case of parotitis, and Martland and Winner (1939) to one of oöphoritis.

Method of spread.—Studying the epidemics as a whole, it can be said that the disease is not spread by water, milk, or food. It is quite clear that the spread is from person to person, and in a very large number of instances it is easy to trace the contact with others who had the disease or developed it shortly after. The contact is nearly always close; frequently relatives or children habitually sitting in the next seat to each other at school or sleeping in the same dormitory. The sole exception to this is in the epidemic described by Bashford (1934) in the London General Post Office, where the contact appeared only casual. The dormitory and family spread suggests a droplet infection.

Degree of infectivity.—The infectivity seems only high when contact is close, as in schools or similar institutions, or in families. Thus Glover (1930), reports that

in three schools 16%, 25%, and 33% of children were affected, but of the total 25 cases 19 were in family groups. A typical example of an epidemic was seen in Wensleydale (Pickles, 1930) where there were 250 cases among a population of 5,700 living in part of a valley less than twenty miles long. Each village had a good and separate water supply. There was constant communication between villages.

The incubation period.—The exact period of incubation is difficult to assess as the period of infectiousness is uncertain. An approximate time, however, can be estimated by studying the early cases of epidemics in homes where contact is close and members of the family often sleep together with little if any attempt at isolation. It is then seen that the cases occur either simultaneously or at spaced intervals of between twenty and forty days or, more probably, between twenty-one and thirty-five days. The following are typical examples :—

(1) A boy, aged 12, returned home from a preparatory school where there had been jaundice and at once developed the disease. His sister, aged 8, fell sick four weeks later ; the father thirty-one days after that ; then the mother after a further thirty days. (Findlay, Dunlop and Brown, 1931.)

(2) A family in a village in Wensleydale.

Aug. 16, 1929.	Jane.
Sept. 14, 1929.	James.
	Sarah.
Oct. 11, 1929.	William.
Oct. 12, 1929.	G. S. (Great friend of the family.)
Nov. 7, 1929.	Ann.
Nov. 6, 1929.	Jennie U. (A little girl, inseparable from the family.)
Dec. 4, 1929.	W. M. (Fiancé of Ann.)
Dec. 2, 1929.	D. U. (2-year-old sister of Jennie U.)
Dec. 29, 1929.	Jno U. (Father of the U. children.) (Pickles, 1930.)

(3) Five patients in three different villages whose only experience in common was that they attended a village fête a month before where they were in contact with a young girl suffering from jaundice. (Pickles, 1936.)

(4) An accidental infection of a laboratory worker as a result of working with serum from the Wensleydale epidemic of 1930. The possible incubation period was between thirty-one and forty-one days.

Dr. Glover tells me that he agrees that many epidemics have this long incubation period but believes that there is a form of the disease with a short incubation period of about four days. He arrived at this conclusion after a very careful study made by himself and Dr. Wilson (Glover and Wilson, 1931) of an extensive outbreak in a country town in which two boys' schools were involved. Many of the cases fell sick on the same day, and he thinks that it would have been very difficult for a disease with a long incubation period to have hit off one day so exactly. There was, however, no direct evidence that the incubation period was short, and they describe a case of a little girl who had been staying in the town who developed jaundice twenty days after leaving it, although there seemed no likelihood of infection during this latter period. As Findlay, Dunlop and Brown (1931) point out, an apparently short incubation period may be explained by A and B having been infected long before by X. Barber (1937) says that he has observed an epidemic in an institution with an incubation period of seven to eight days, but gives no details. Personally, I believe the evidence to be overwhelming that the incubation period is approximately between three and five weeks.

Period of infectiousness.—There is ample evidence that patients are infectious before they are jaundiced. The actual period of infectiousness must be short as shown by the extraordinary periodicity in families and small villages where there is little isolation and cases, often single, occur in series at an interval of about a month.

It is probably quite safe to return the children to school after two weeks. In adults, I do not hesitate to admit cases to the general wards of a hospital when jaundice is once established.

Carriers.—Sometimes unexplained gaps appear in an epidemic. For instance Newman (1939), who has studied an outbreak in the southern part of Sussex, found that it started in Arundel and Billinghurst at the end of 1937, died out shortly, recurred in different parts of the county in the summer of 1938, again died down, and then became established in October 1938 and still continues. It may be that there are carriers. Dr. Newman tells me that he has observed two separate cases arising where there could have been no possible contact with other patients. However, both had been in contact with people who themselves might well have been in contact with the disease.

Certainly, many cases are missed. Dr. Newman says that jaundice was found when looked for which would not have been identified as such under different circumstances. Moreover, in his epidemic, as in others, there are cases with initial symptoms followed by dark urine, without subsequent jaundice, and cases with initial symptoms with neither dark urine nor jaundice. The early appearance of bile in the urine is of importance. It may be fleeting, as shown by the following case described to me by Dr. A. W. Franklin (1939). It was at a time when he was seeing two or three cases of jaundice a week in the out-patient departments of two London hospitals. A child who had been vomiting and unwell for a few days, had a slightly tender liver but no jaundice. In the morning there were bile pigments in the urine; in the afternoon they had disappeared. The child made a quick recovery. These missed cases, the possibility of a carrier spread, the long period of incubation and sometimes the low infectivity, may explain why the disease is endemic in certain areas, and also why many cases appear to be sporadic. With regard to isolation, all children in schools with bilious attacks and vomiting during an epidemic should be isolated for a few days to see if they develop jaundice. No causative agent has been discovered. Leptospiral infection has been excluded. No convincing bacterial cause has been found. The disease cannot be transmitted to ordinary laboratory animals. These facts, together with the long incubation period, the clinical picture, and the absence of leucocytosis, suggest that the disease may be due to a virus infection.

Pathological Process of Common Infective Jaundice

The pathological process is probably, as was first suggested by Flindt in about 1890, a necrosis of the liver cells. Direct proof of this is difficult to obtain as opportunities for post-mortem examination of undoubted and uncomplicated cases of common infective jaundice are rare. Occasionally, however, during epidemics apparently typical cases adopt a severe clinical course ending in death. Two such cases in this country were reported by Morgan and Brown (1927) and Findlay and Dunlop (1932). Post-mortem findings showed liver-cell damage with no evidence of obstruction or infection of the bile-ducts. The criticism could be made that this was really a complication of the initial disease. A few descriptions appear in the literature of similar findings in cases in which a piece of liver had been removed for section at operation; for example Schrumpf (1932) and Nordmann (1925). Fortunately, there are two reports of patients who died as result of accidental death who at the same time appeared to be suffering from ordinary mild common infective jaundice. The first of these was reported by Gaskell (1933).

A girl, aged 5, was admitted to hospital for removal of tonsils and adenoids. The operation was performed under ether anæsthesia. The next day the child was jaundiced. On the following day, as a result of secondary hæmorrhage from the tonsillar bed, the patient died. In the village from which the child came there was at the time a true epidemic of infective jaundice and other

cases occurred both before and after the one described. At post-mortem examination there was general infiltration of Glisson's capsule with inflammatory cells. The liver parenchyma was swollen and degenerate. The bile epithelium was normal.

The details of the second case, as yet unpublished, have kindly been sent to me by Dr. H. Barber. The post-mortem material was studied by Dr. G. R. Osborn.

The case occurred in 1937 in Derbyshire where the disease was endemic. The patient, a man, aged 38, started his illness with nausea and vomiting. On the same day he fractured his skull. Four days later he was jaundiced, and on the eighth day he died as a result of the fracture. The liver showed early hepatitis without inflammation in the bile-ducts or duodenum.

Recently the view propounded by Virchow that common infective jaundice is really due to obstruction of the mouth of the common bile-duct has been revived by Hurst and Simpson (1934). They divide common infective jaundice into two diseases, one a true catarrhal jaundice due to temporary obstruction of the bile-duct, and the other a mild primary hepatic necrosis. They consider that there is clinical, biochemical, and histological evidence for this distinction. They say that in true catarrhal jaundice there is an initial gastritis with complete anorexia and nausea or vomiting, flatulence, epigastric discomfort, and pain, sometimes diarrhœa, furred tongue, and slight fever. The gall-bladder may be palpable when the patient is jaundiced. On the other hand, cases of mild primary hepatic necrosis seldom show pre-icteric symptoms of any kind, and the onset of jaundice is accompanied by symptoms of toxæmia such as headache, weakness, loss of appetite, and occasional vomiting and diarrhœa. There is slight fever, no epigastric tenderness, the liver is tender and slightly enlarged, the spleen is always palpable. Jaundice is less marked than in " catarrhal jaundice " and bile is always present in the stools. The condition lasts longer than true catarrhal jaundice.

In my experience, however, in a single epidemic both clinical pictures may be found at the same time. For instance, jaundice may appear from 0 to 12 days after the onset. Further, I have seen cases of subacute necrosis of the liver in which there was no suggestion at necropsy of obstruction or inflammation of the bile-ducts which had just such a history of initial gastritis as is described in the true "catarrhal jaundice". In these, the stools were often clay-coloured in the early stages. The spleen was only palpable in less than a third of the cases. Hurst and Simpson say that in true catarrhal jaundice the lævulose tolerance test was normal in nine out of ten patients, whereas in a case of primary hepatic necrosis there was evidence of hepatic insufficiency. But it is generally agreed that an impairment of lævulose tolerance depends on the degree of liver damage, and that this damage must be extensive before changes in tolerance are found. In one of the cases of subacute necrosis to which I have referred, the lævulose tolerance test was normal in the first attack of jaundice and impaired in the second.

In my opinion the van den Bergh test is of no value in distinguishing between jaundice caused by obstruction and jaundice caused by parenchymal damage of the liver cells.

Finally it is said that in true " catarrhal jaundice " the parenchymal necrosis is mainly in the central zone of the lobule, and that obstruction of the bile-ducts with cholangiectasis is a condition which constantly brings about such a central necrosis by pressure alone. With this I agree, but an initial central necrosis is also the outstanding characteristic of primary acute necrosis of the liver where there is no question of obstruction. Fig. 1 is a section taken from the liver of a patient who died from acute liver necrosis in pregnancy. The centres of the lobules are acutely fatty ; the cells at the periphery are relatively normal. Fig. 2 is a section from another case of acute necrosis in pregnancy and shows extensive degeneration of the lobules, especially in the centre.

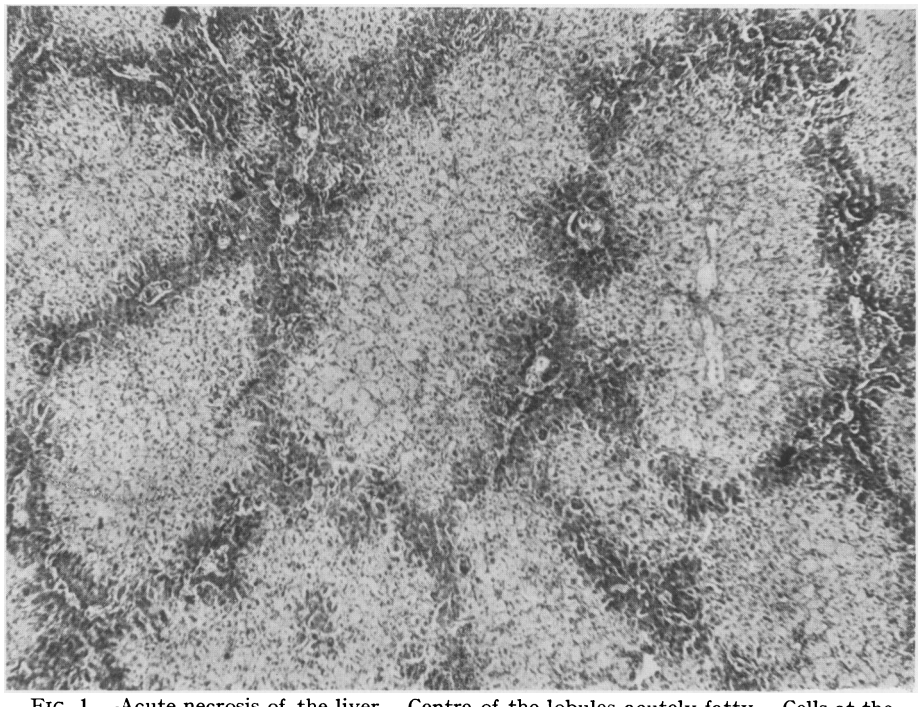

FIG. 1.—Acute necrosis of the liver. Centre of the lobules acutely fatty. Cells at the periphery relatively normal. (× 50.)

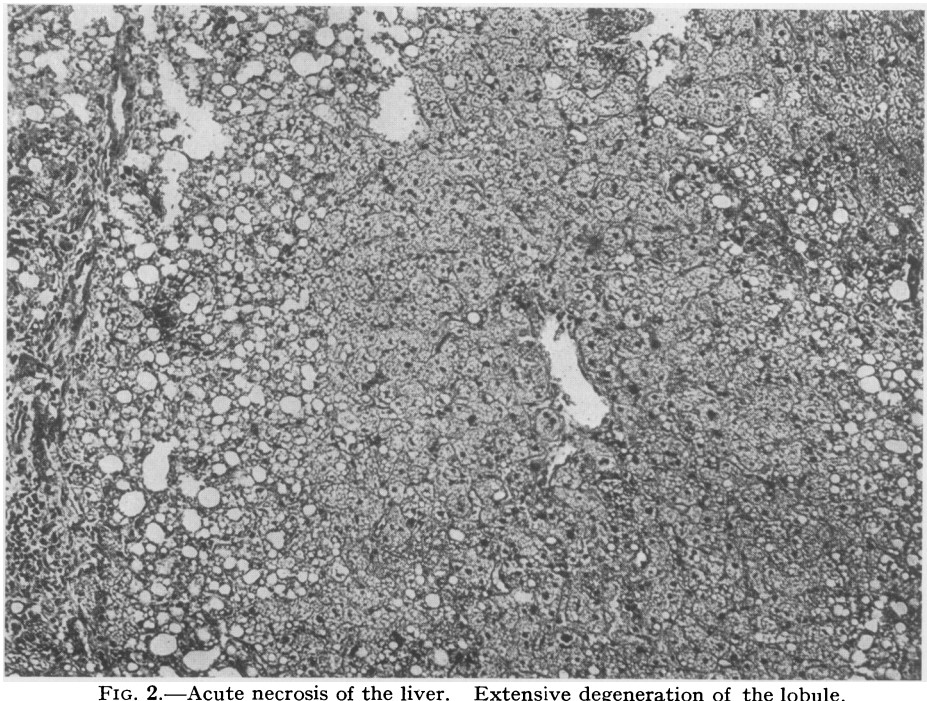

FIG. 2.—Acute necrosis of the liver. Extensive degeneration of the lobule, especially in the centre. (× 100.)

Figs. 1 and 2 from St. Bartholomew's Hospital Reports, 1936, **49**, by permission of the Editors. Blocks kindly lent by Messrs. John Murray, Ltd.

I do not believe that there is convincing evidence that common infective jaundice, as seen in Britain, has two separate pathologies. The much-quoted Gallipoli epidemic is hardly a fair criterion. The exact nature of this epidemic, occurring in a population saturated with paratyphoid B, was never settled. Such knowledge as we have of the disease in this country points to the jaundice resulting from damage of the parenchymal cells of the liver and not from a blocking of the common bile-duct or an ascending cholangitis. If the two conditions do exist, I should regard them as clinically indistinguishable from each other.

The Relation of Common Infective Jaundice to Acute and Subacute Necrosis of the Liver

Occasionally common infective jaundice ends with severe liver necrosis and death. I have already referred to two such cases in this country (Morgan and Brown, 1927 ; Findlay and Dunlop, 1932). In Sweden, Bergstrand (1930) reported a large number of instances. In Stockholm, between the years 1914 and 1925, there were on the average two cases a year of acute yellow atrophy. In 1925 and 1926 epidemic jaundice was rife throughout the country. In 1926 the incidence in Stockholm of acute yellow atrophy increased and in 1927 there were 42 cases. It might be said that epidemic jaundice in Sweden is not comparable with the disease seen in England. I am going to suggest that subacute necrosis of the liver unassociated with any known drug or toxin is in fact quite frequently seen in this country. In 1936 (Cullinan 1936) I published an account of 20 cases with post-mortem findings. These had been found mostly in one large London teaching hospital. Since that time I have seen many more proven cases and a larger number in which the diagnosis was made on clinical evidence alone. The clinical picture is remarkably similar, apart from its greater severity, to that of common infective jaundice.

The disease is characterized by attacks of jaundice. The attacks are often accompanied or preceded by vague symptoms of ill-health and gastric disturbance. These initial symptoms seldom persist after the jaundice is fully established.

During the height of the attack the patient feels moderately well. There is no fever, no mental disturbance, no loss of weight, and rarely any pain. Occasionally there is nose-bleeding.

There is usually enlargement of the liver and sometimes of the spleen. The colour of the stools varies from time to time but is seldom clay-coloured when the jaundice is established. Bile is found in the urine. There is moderate anæmia, but no leucocytosis. Van den Bergh's test is positive, both direct and indirect. Tolerance to lævulose is lowered. On X-ray examination the gall-bladder fails to concentrate dye.

The intensity of the jaundice varies in different cases and tends to fluctuate during the course of the disease. The jaundice may last for weeks or months. If the attack is not fatal, recovery may be complete, but after a period of good health varying in time from a few weeks to many years, the jaundice may recur.

In cases of long standing there may be hæmorrhages and signs of ascites.

When the attack is fatal, death usually results from liver failure, the symptoms and signs of which appear only in the last few days of life.

Histologically, there is subacute necrosis of the liver parenchyma affecting particularly the centre of the lobules. The bile epithelium is seldom destroyed, and the extralobular bile capillaries stand out prominently. The bile-ducts in the liver are not dilated and do not contain bile. There is no evidence of obstruction or inflammation of the larger bile-ducts.

In the absence of further epidemiological data it is difficult to say whether some or all of these cases are directly related to common infective jaundice. Subacute necrosis is caused by many agents, and although the cases here reported appear identical in their clinical and morbid anatomical appearances with those described by Bergstrand, this does not prove the relationship. The similarity, however, between these cases of subacute necrosis of the liver and cases of common infective jaundice is so close as to suggest that one of the causes of subacute necrosis is identical with the cause of common infective jaundice.

Relation of Common Infective Jaundice to Jaundice Observed in a Diabetic Clinic

Graham (1938) described an outbreak of jaundice in a diabetic clinic of a London hospital. The first case was noticed in May 1935, and during the next two and a half years there was a series of 28 cases. The epidemic has now ceased, and there have been no further cases in the last year. The patients in this clinic sat closely together on a bench in the out-patient hall. Graham points out that similar experiences have not been had in other diabetic clinics in London. The symptoms were identical with those of common infective jaundice except that the jaundice persisted for a long time and the diabetes was made worse. The shortest duration of jaundice was thirty-one days and the longest ninety.

It would appear that these were cases of common infective jaundice. It is possible that the greater duration of the disease in these patients may have been associated with a lowered resistance of the liver.

Relation of Common Infective Jaundice to Jaundice following Injections of Arsphenamine

There is no doubt that certain drugs given in large doses are sometimes followed by jaundice and necrosis of the liver. One example is salvarsan and its derivative used in the treatment of syphilis. Many years before the introduction of salvarsan it was known that syphilis was sometimes accompanied by jaundice and acute necrosis of the liver. Weber (1909) gives a bibliography of 53 cases up to the year 1908. Since the introduction of salvarsan the incidence of jaundice has risen. Thus Wile and Sams (1934), surveying the treatment of over 10,000 cases of syphilis, found that jaundice occurred seven and a half times more frequently in those patients who had been given salvarsan than in those who had not. The interesting feature is that a large number of cases of so-called post-salvarsan jaundice occur in epidemics irrespective of the preparation of the drug or the way in which it is given. Stokes, Reudemann and Lemon (1920) say that of 5,200 cases of syphilis treated in the Mayo Clinic from August 1916 to July 1920 there were six cases of jaundice in the first two years and 64 in the second. The methods of treatment over the four years were the same. Similar experiences are reported from other parts of the world. Bodin (1921), in France, found that in 254 cases of syphilis treated with arsenobenzols between the years 1912 and 1914 there were only two cases of jaundice. In 1921, 472 patients were treated and there were 34 cases of jaundice. Ruge (1925), reviewing the incidence of jaundice in the German Navy, states that the number of cases of epidemic infective jaundice rose considerably in the years from 1919 to 1923. Parallel with this rise there was a similar increase in the number of cases of so-called salvarsan jaundice without any alteration in the mode of treatment. Thus, of all syphilitic patients under treatment: in 1919, 3·7% developed jaundice; in 1920, 7·14% in 1921, 12·70%; in 1922, 10·60%; and in 1923, 20·37%. He suggests that so-called salvarsan jaundice is really ordinary infective jaundice in which syphilis and salvarsan occur as supporting agents in the origin of the disease. There were no clinical differences between the ordinary infective jaundice and the post-salvarsan cases except that the latter tended to be rather more severe and of longer duration. Richards (1933), gives an interesting account of an epidemic in the venereal clinic of a hospital in the Midlands. Commencing in April 1931 there was a series of over 120 cases of jaundice among patients receiving antisyphilitic treatment with salvarsan derivatives. The number of cases was in a ratio of one in every three. The great majority occurred among men. The disease in some was very mild, but in others sufficiently severe to require in-patient treatment. Sometimes the jaundice came soon after an injection, but in a few it was not until several months had elapsed. Alterations were made in the preparation of the drug without result. Eventually

jaundice appeared in a man who had received bismuth alone. The patients had to wait in a crowded passage and in 1932, owing to a great increase in the number requiring treatment, the crowding became acute. As soon as efforts were made to avoid excessive crowding there was a definite drop in the number of cases of jaundice. In August 1933 it was decided that all patients must wait in a large and well-ventilated out-patient hall and be admitted to the clinic in small numbers. The immediate result of this was a rapid fall in the incidence of jaundice.

Jaundice following arsphenamine is frequently delayed. Wile and Sams (1934) found that two-thirds of their cases occurred at an average interval of eighty days after the last injection had been given. However, as shown by Richards, the time after the last injection that the jaundice appears is by no means constant. Todd (1921), recording experiences in the Rhine army, says that he saw no cases of jaundice in patients having arsphenamine during the period from March to September 1920, but in October 1920 there were 24 cases with one death. The time of onset after the last injection varied from 1 to 119 days.

It is not suggested that jaundice cannot be produced by arsphenamine alone if a large enough dose is given. It seems clear, however, that a great number of cases of ordinary post-arsphenamine jaundice occur in definite epidemics and at the same time as epidemics of common infective jaundice. The interval between the onset of jaundice and the last injection of the drug is widely variable. Considering these facts, together with the similarity between the clinical and epidemiological features of the diseases, it would appear that post-arsphenamine jaundice is often identical with common infective jaundice. The greater severity of the clinical symptoms suggests that syphilis and salvarsan are supporting agents, which render the liver more susceptible in the origin of the disease.

Relation between Common Infective Jaundice and Jaundice following Inoculation against Certain Diseases

(*a*) *Yellow fever post-inoculation jaundice.*—Findlay and MacCallum (1938) recorded that among 3,100 persons immunized against yellow fever with virus and homologous immune serum over a period of five years, 89 cases of jaundice had been traced. The interval between the inoculation and the onset of jaundice varied from thirty-six days to just under seven months : the average interval was between two and three months. The cases almost always tended to occur in groups in regional areas. The disease was not yellow fever, and the symptoms closely resembled those produced by common infective jaundice, cases of which have frequently been noted as occurring in the same areas.

In two instances the syndrome started four weeks after exposure to infection with common infective jaundice. In a recent paper Findlay, MacCallum and Murgatroyd (1939) say that since another strain of the attenuated tissue culture virus has been used no jaundice has occurred among the 2,500 people inoculated. They give evidence to show that an extraneous hepatotoxic agent having many of the characters of a filtrable virus had been introduced into the former yellow-fever vaccine by the vehicle of apparently normal human serum. They postulate that this agent, probably a virus, is identical with the causative agent of common infective jaundice. They make the important recommendation that pools of apparently normal human serum should not be used for human inoculation, unless the medical history of all the donors can be followed for at least one month. One would suggest that this period should be extended to six weeks and that the donors should have no history of jaundice in the past.

(*b*) *Measles post-inoculation jaundice.*—A similar outbreak has been seen after inoculation against measles. MacNalty (1938) reports that among 82 to 109 persons inoculated with human serum from one batch there were 37 cases of jaundice, seven of which were fatal. More recently a further series occurred. A widespread inquiry

was made in this country, in Europe and in America, but no similar sequence of events could be traced. The report refers to these cases as acute infective jaundice not to be confused with epidemic catarrhal jaundice, but as I have said, I do not believe that the distinction can be made. Jaundice appeared from 16 to 100 days after the inoculation. The symptoms and physical signs of the majority differed little from those of the so-called " epidemic catarrhal jaundice " which had been prevalent in the district mainly affected. The same conclusions can be drawn as in the yellow-fever post-inoculation cases, that a hepatotoxic agent was present in the apparently normal human serum, and that the same precautions in administration are necessary.

There seems little doubt that both yellow-fever and measles post-inoculation jaundice are identical with common infective jaundice. But the jaundice develops at widely varying times after the inoculation, usually long after the normal incubation period of common infective jaundice and also the cases occur in areas where common infective jaundice is known to exist. It seems possible that a hepatotoxic agent, perhaps a virus or substance in the serum of donors who have or have had common infective jaundice, was introduced by the inoculation, and that this agent did not itself cause but predisposed to a subsequent infection of the disease, often in a more severe form.

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Discussion.—Dr. J. D. ROLLESTON said that though he could not claim much practical experience of epidemic jaundice, his interest in the subject had been shown by his summaries of the literature in the *Medical Annual* for the last twenty years. Recent articles had drawn attention to the increasing frequency of leptospiral jaundice in Great Britain, especially among sewer-men, miners, and fish-workers, and had suggested the employment of prophylactic measures such as inoculation and the destruction of rats (Rees). Abortive forms simulating aseptic meningitis in which no jaundice was present were frequent, and could only be diagnosed by an agglutination test. Dr. Rolleston inquired if any members had had experience of leptospiral jaundice following bathing, of which numerous examples had occurred in Holland, where the closure of the swimming bath at Dordrecht, one of the towns most affected, was followed by a remarkable fall in the incidence of the cases (Jitta).

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Dr. J. L. NEWMAN said that an endemic focus of jaundice was found to have existed in Arundel since July 1937, but it did not spread outside till April 1938. Since then seven widely separated foci had appeared in the North; but the main spread has been along the coastal plain, and so to ten centres, with a particularly heavy incidence in the Bognor district.

There had been two seasonal peaks, one in November (60 cases) and one in January (87 cases). As in the Medical Research Council Report there had been little tendency to spread in schools, and of the 39 involved, 20 had produced three or less cases, and only four 25 or more. The important role so often attributed to schools in favouring spread might be more apparent than real and due to the age of maximum incidence being 6–10 years.

Two particular outbreaks had been mentioned. At Slindon, the village as a whole escaped, and there was no spread in the school. All the cases were concentrated in a single row of houses just outside the main village, and the proportion of adults attacked was relatively high: seven school children, one adolescent, four adults. At Aldingbourne there had been 65 cases involved over a wide area. Spread seemed to have been entirely through the school (55 cases out of 180 children): another small school close by was not involved till the outbreak was over, and adjacent and contiguous villages escaped entirely. The classroom might have had some influence since the infants' room was not involved till seven weeks after the onset. Direct contact was likely in most cases, but two suggested the possibility of carriers.

(1) An isolated cottage used as a home for low-grade mentally defective children (mostly cot cases) had one case. The two attendants had been well and the parents came from an uninfected district. Bottled milk was delivered by a boy who had the disease thirty-one days before, but none of his other customers was infected.

(2) A remote cottage said to have been entirely cut off by the very bad weather at Christmas had 2 cases. Two children attended the village school and remained well. Their brother, aged 4, had been confined to the house with a severe attack of impetigo for six weeks before, on January 14, he sickened with jaundice. His father sickened one week later.

Atypical cases might be of epidemiological importance. In three schools the teachers volunteered the information that there had been an unusually high rate of absence for " biliousness " before the jaundice cases appeared. Among the atypical cases quoted were :—

(1) Eileen W. October 5 sickened for a typical attack.
Norman W. October 25 sickened for a typical attack.
Mrs. W. November 13 vomited all day, poorly, ached all over. 14th better, but sharp abdominal pain. Later the urine was dark, stools clay coloured, and the family noticed just perceptible jaundice ; the patient would not have noticed this herself.

(2) George H., aged 7. December 20 sickened for a typical attack.
Susan H., aged 4. January 17 sickened for a typical attack.
Mrs. H. February 17–20 vomiting, anorexia, and malaise. No pain or evidence of bile.

Dr. Newman summarized his observations as follows :—

(1) " Biliousness " may precede an outbreak of jaundice.

(2) School outbreaks tend to fizzle out without serious spread : the liability to spread in schools has been overrated.

(3) House-to-house infections may occur but are relatively unimportant.

(4) Carriers may provide the means of propagation.

(5) Atypical cases, recognized as jaundice only in the presence of other cases, or even unrecognized, may be of epidemiological importance.

(6) Clinical features were so variable as to make futile any attempt to differentiate by their means different types of upper abdominal disease.

Major H. C. BROWN said that he was glad to hear that Dr. Cullinan did not advocate the subdivision of epidemic catarrhal jaundice into two distinct diseases.

He would like to ask Dr. Cullinan what his views were on the degree of immunity conferred by an attack of this disease. Working with Dr. Morgan in the Northamptonshire epidemic, they were of opinion that villages showing a high rate of infection one year showed few cases in the following year.

Dr. Cullinan had referred to jaundice following the administration of measles immune serum and also to the necessity for accurate diagnosis as early in the disease as possible. He had had the opportunity of examining one of the earliest cases of jaundice after measles serum ; this case had been diagnosed as being Weil's disease, but from the total absence of antibodies to the *Leptospira icterohæmorrhagiæ* and from the results of animal inoculation, he was able to exclude Weil's disease. Furthermore, in this case, the absence of leucocytosis and the high mononuclear differential blood-count pointed very strongly to the condition being one of epidemic catarrhal jaundice.

He would finally like to ask Dr. Cullinan whether he knew of any clinical symptoms or physical signs which would enable anyone to differentiate between a really florid case of epidemic jaundice and one of Weil's disease, as apart perhaps from the intense muscular pain in the latter he thought that the differential diagnosis on purely clinical grounds was extremely difficult if not impossible.

Dr. J. A. GLOVER agreed the evidence that one type of epidemic catarrhal jaundice had a long incubation period seemed conclusive. He suggested there was a second type with a short incubation period, in which tonsillitis was often a prominent symptom, and in which cases of tonsillitis without jaundice were seen alongside the cases of jaundice. Such seemed to be the epidemics described by Chomet in Vienna in 1933, by Dr. J. Wilson and himself in Dorset in 1930, and that at Burton-on-Trent in 1935 by Dr. E. M. R. Frazer, in which in every case of the 25 described there was a common symptom of sore throat. Dr. Frazer, however, had not stated the incubation period. H. Barber had been fortunate enough to observe two epidemics

of catarrhal jaundice in one institution, the first with a short (seven to eight days') incubation, the second with one of twenty-five days.

He contrasted with these the Woolplumpton epidemic of 1930 reported by Dr. Brothwood, in which no sore throat was reported, or the long incubation type epidemic at Newbold Verdon in 1936 reported by Dr. A. A. Lisney, where only one out of 40 cases had sore throat. Dr. Glover

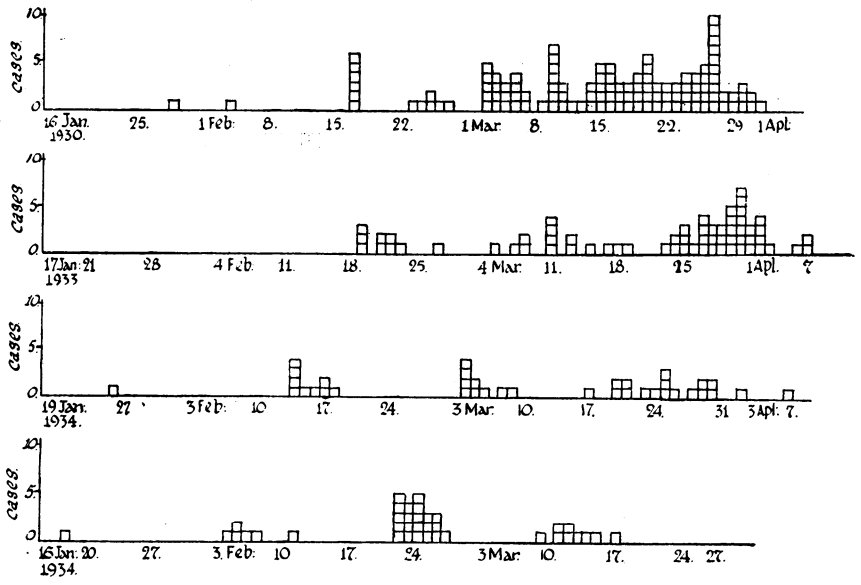

FIG. 1—Showing the daily incidence of cases of mumps in four epidemics. (From "Epidemics in Schools," Spec. Rep. Ser. Med. Res. Coun., 1938, No. 227, p. 161. Reproduced by permission of the Controller of H.M. Stationery Office.)

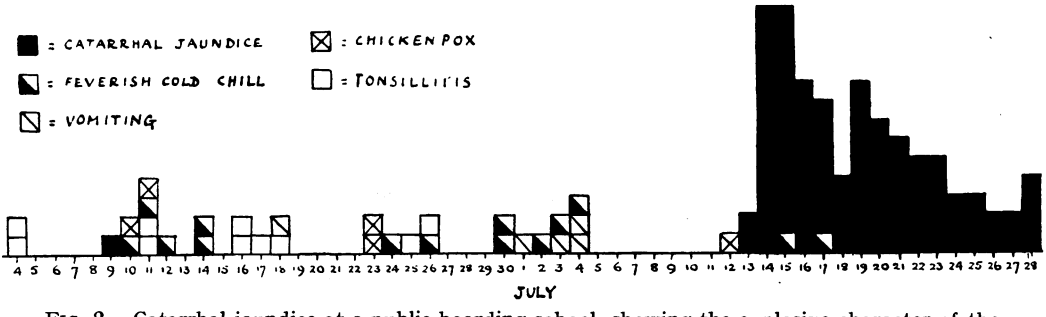

FIG. 2.—Catarrhal jaundice at a public boarding school, showing the explosive character of the epidemic. (*Lancet*, 1931 (i), 722. Reproduced by permission.)

showed three diagrams, the first (fig. 1) giving four typical daily incidence charts of school epidemics of mumps, a disease which has the same incubation period as the long incubation type of epidemic catarrhal jaundice. He pointed out the straggling incidence in all these epidemics (characteristic of a disease whose incubation period may vary by as much as a week) compared with the almost explosive incidence shown in the daily incidence chart (fig. 2) of the short

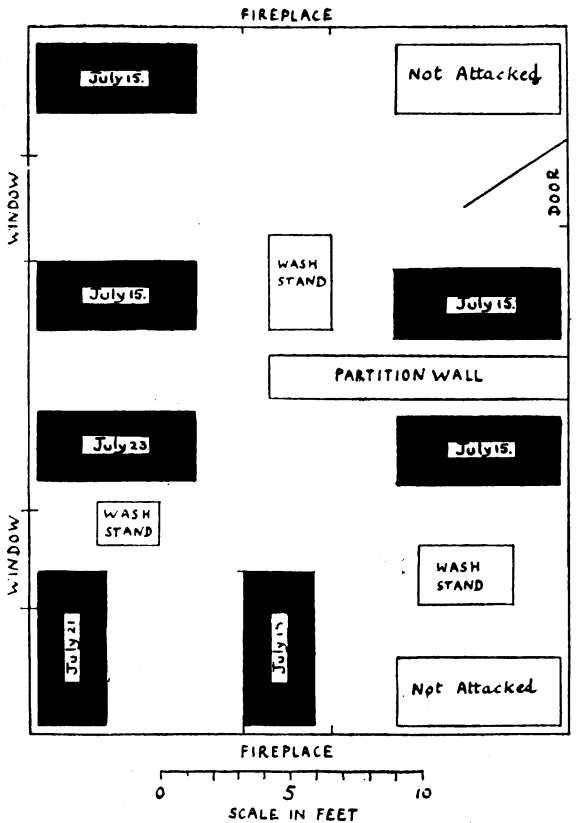

FIG. 3.—Plan of dormitory in which seven out of nine boys were attacked. From *Lancet*, 1934 (i), 724. (Reproduced by permission.)

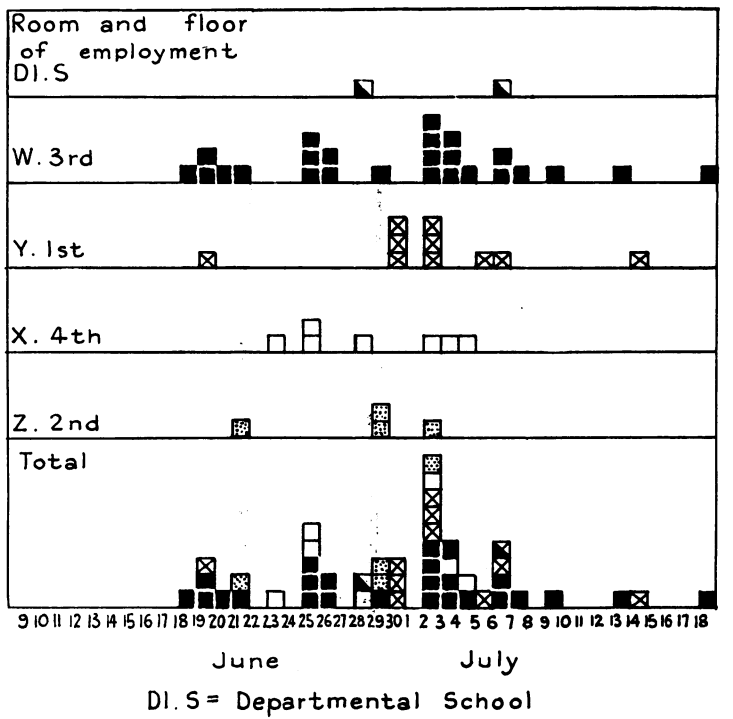

FIG. 4.—Epidemic of catarrhal jaundice in certain rooms at the General Post Office, June-July, 1934. (From Tables by H. H. Bashford, *Lancet*, 1934 (ii), 1008.)

period catarrhal jaundice epidemic described by Wilson and himself. The extreme steepness of the epidemic wave in the latter was much more like that of an influenza epidemic. The third diagram (fig. 3) showed the incidence in one dormitory during the same epidemic. Nine boys slept in the dormitory, seven of whom were attacked ; in five cases the onset was on the same day, in the sixth there was an interval of six days, followed in two days' time by the seventh.

Dr. Glover also showed a chart of daily incidence by rooms, constructed from the details given by Sir Henry Bashford (fig. 4) of the epidemic of catarrhal jaundice at the General Post Office in 1934. Thus dissected, the incidence might be interpreted in favour of a short incubation period. The occurrence of missed cases and cases " sine eruptione " and the possibility of carriers in all epidemics, made the determination of incubation period exceedingly difficult.

There might be a third type, of which the extensive epidemic at Mount Allison University recorded by Roy Fraser [1] was an example. This epidemic was closely associated with an epidemic of gastro-enteritis due to a Salmonella infection.

Dr. J. M. ALSTON said that Dr. Cullinan spoke of vaccination for preventing leptospiral jaundice in people whose occupation or pursuits made them liable to this infection. He did not think the other means were worth consideration. The results of vaccination on a large scale in Japan were not clearly decisive in favour of it and there were some severe reactions to the vaccine. In this country, Dr. John Smith vaccinated some children and produced antibodies, but of a rather low titre. From another aspect among London sewer-men, who form one of the largest groups of men exposed to this risk in Great Britain, the morbidity rate is only 1% per annum, so that there must be some doubt whether the result of vaccination could justify the time, expense, and risk involved. In occupations in restricted premises, such as fish-curing, Dr. Alston said it would seem that good hygiene should banish the infection.

Dr. W. N. PICKLES said that instances of hepatic necrosis appeared in mild epidemics and seemed to have a common ætiology and incubation period. Close contact—e.g. sharing a bed—seemed to be a factor in the transference of infection. He showed a chart on the screen of a recent epidemic in his practice, which strengthened the evidence of a long incubation period.

He asked Dr. Cullinan if he had evidence of permanent damage to the liver in patients who had suffered from this disease.

Dr. G. M. FINDLAY said that until the causal agent or agents had been identified and isolated, there would continue to be uncertainty as to the number of conditions included under the designation of infective jaundice. One form of infective jaundice was undoubtedly associated with an acute hepatitis, and evidence recently obtained strongly suggested that this hepatitis was due to the action of a virus (Findlay, MacCallum and Murgatroyd, 1939). Following immunization against yellow fever, 95 cases of jaundice had been traced among 3,100 persons inoculated with an attenuated strain of yellow-fever virus grown in tissue culture. By eliminating various factors and finally by changing the strain of yellow-fever virus employed, this jaundice, which resembled in every way common infective hepatic jaundice, had now been eliminated and no case had occurred in more than 3,500 persons. Evidence suggested that the virus had been introduced into the tissue cultures with apparently normal serum. This was strictly analogous to the occurrence of jaundice following immunization against measles. In the jaundice following both measles and yellow-fever immunization, the incubation period had been longer than that usually associated with common infective hepatic jaundice. It must, however, be remembered that the incubation period of many virus infections, rabies for instance, showed very great variation, more especially when the virus was introduced by an abnormal route. Both the measles and yellow-fever jaundice cases had shown a tendency to be collected in little groups, but it was uncertain whether this was due to factors peculiar to a particular place or to random distribution of susceptible persons. One great difficulty in establishing the virus ætiology of infective hepatatis was the failure to infect a laboratory animal. Recently, however, it had been possible to obtain a febrile reaction in rhesus monkeys by feeding them by stomach tube with whole blood obtained

[1] *Canadian Pub. Health J.*, 1931, **22**, 396.

from cases of jaundice in the early stages. To establish whether this reaction in monkeys was due to a specific infection or not, blood from early further cases of jaundice was urgently required.

The view that jaundice was a contagious disease was of very long standing. Zacharias, who was Pope from A.D. 741 to 752, writing to St. Boniface in Germany, strongly recommended that patients with jaundice should be segregated lest others catch the contagion (cf. Migne: *Patrologia latina*, **89**, 951).

Reference.—FINDLAY, G. M., MACCALLUM, F. O., and MURGATROYD, F. (1939), *Tr. Roy. Soc. Trop. Med. & Hyg.*, **37**, 575.

Dr. J. W. HEALY said that with a view to learning more about the prevalence and clinical features of epidemic jaundice amongst children of school age in L.C.C. schools, residential schools, and special hospitals, at the beginning of last year district medical officers were asked to report on all children excluded from school on account of jaundice, on other children in the school suffering from the disease, and on the possible source of infection in each case. Later, this was further systematized by circulating a questionnaire to ascertain in addition the date of onset, clinical features, duration of illness, and hospitalization.

Over the period November 1937 to February 1939, 193 cases of jaundice were notified in this way. Some of the data, however, were unreliable, and many mild cases must have been missed. 70% of cases in the series could be linked up with some other or others in point of time, but incubation periods could not be worked out in day-school outbreaks, where knowledge of the conditions and duration of contact was lacking. In one special hospital ten cases occurred in one ward, four crops following the primary case, and there were five intervals of 25–28 days, two of 32, one of 35, and one of 16 days.

The largest school group was in the Isle of Dogs, the first two cases occurring at the end of December 1937, and 22 more were strung out over the first three-quarters of 1938. Some irregular clustering of cases within a few days' interval was observed in this series, and there were two long gaps of six weeks each, possibly due to school holidays or to a missed case. In two of the smaller school epidemics all the recorded cases were close together in time, viz. five cases in three weeks in one instance, four cases in eleven days in the other; perhaps examples of the explosive type of epidemic, but complete information is lacking, and there probably were a number of missed cases.

In the Isle of Dogs series there were two groups of children attending the same school and living in the same house. In one of these the time intervals between successive cases were 30, 21, 29, 25, and 27 days, being sufficiently constant to individualize the group, the contact conditions being known and supporting Pickles' deduction that the period of infectivity is relatively short.

Dr. Healy went on to say that the most common symptoms of the pre-icteric stage were drowsiness, headache, and vomiting. In 76 returns the duration of this stage was stated, and in 90% of them it lay between one and eight days. In 12 instances the stage lasted only one day, in one it lasted thirteen days, while in three there was apparently no prodrome. In 46 returns the duration of jaundice was given. In two-thirds of these the limits lay between seven and twenty-one days, in four instances it lasted a month, and in one, six weeks.

The cases were mild and there were no deaths. 33 children, i.e. between one-fifth and one-sixth of the series, were admitted to hospital, the remainder were treated at home.

In about half of the cases (52) in which the period of absence from school could be ascertained, it lay between two and four weeks. The shortest periods of absence were two of seven days each and the longest three of three months each, although coincident chorea may have been partly responsible for the prolonged absence in one of those cases.