Clinico-pathological Conference

LIVER DISEASE IN INFANCY

Held at the Royal Alexandra Hospital for Sick Children, Brighton

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DR. BOURNE: Ladies and Gentlemen, the staff of the Royal Alexandra Children's Hospital has monthly Clinico-Pathological Conferences.

A large number of general practitioners attend these meetings, and I welcome them again to this special one, and also the practitioners from elsewhere who are at the moment attending the general practitioner course, of which we, the local Hospital Group, run several every year.

Tonight, in addition to Dr. Trevor Mann, Dr. Frank Nash and Dr. Keith Elliott, the usual main participants, we are honoured with the presence of Professor Sheila Sherlock, for tonight five cases of liver disease are being presented. Two of these are of an unusual form of liver disorder, the investigation of which was shared with Great Ormond Street. The other three are purely home products, involving a rather peculiar liver lesion with puzzling clinical presentation. Professor Sherlock will, no doubt, produce some new information and philosophy.

Ladies and Gentlemen, I declare the battle open

DR. MANN (*Pædiatrician, Brighton, Lewes and Mid-Sussex Hospital Groups*): I am going to tell you about two sisters, both of whom died within 18 months of each other in early infancy from sudden and catastrophic illnesses which have, as you will see, many similar features.

First I will tell you about K. H., a female infant, who was admitted to the Royal Alexandra Children's Hospital, Brighton in August 1956 at the age of 4½ months and who died the same day. Her birth was normal at full-term in one of our maternity units and her progress during the lying-in period had been uneventful. I must mention that there had been no noticeable jaundice. At the age of 14 days, having been home only a few days, she was admitted to the Children's Hospital because of umbilical bleeding. Hæmostasis was quickly achieved with the help of Stypven and pressure, and as she seemed otherwise well, the baby was discharged home 48 hours later.

The day before her second and final admission to the Children's Hospital at the age of 4½ months the baby developed some areas of bruising over the left side of the body and 24 hours later was urgently referred to hos-

pital because of right-sided 'twitching'. She had by this time stopped feeding and was vomiting. A week previously she had attended our dermatological outpatient department because of multiple capillary naevi for which Thorium-X was ordered.

On examination she was an ill but well-nourished child who showed pallor and some jaundice. Three small bruises were evident over the left side of the body. There was no enlargement of the liver or spleen. The baby seemed conscious. The anterior fontanelle was bulging. The right arm and leg were hypotonic. Later on the day of admission she deteriorated rapidly, showing increasing pallor, a left-sided ptosis and facial palsy. Fundal examination at this stage revealed papilloedema and retinal hæmorrhages. The subdural space on both sides of the skull was needed and no blood obtained. A lumbar puncture revealed xanthochromic slightly blood-stained CSF under very increased pressure, containing 4 leucocytes/cu.mm., 13,500 r.b.c./cu.mm., protein 650 mg./100 ml., and sugar 79 mg./100 ml.

DR. ELLIOTT (*Pathologist, Royal Sussex County Hospital, Brighton*): At post-mortem the major findings were in the brain. There was a large hæmorrhagic mass in the left frontal region which was pushing the brain out of the way and measured about 4 cm. in diameter. Other organs which were examined seemed perfectly normal. A confident diagnosis was made of a frontal tumour and the report given to the coroner was to that effect. When sections were cut, however, a very different picture emerged. There was no sign of any cerebral tumour whatever. The mass in the frontal lobe was blood clot, with dilated vessels here and there which appeared abnormal in number and calibre, so a revised diagnosis of cerebral angioma was made.

Another unexpected finding was the microscopical appearance of the liver. At autopsy no jaundice was noticed, and to the naked eye the liver had seemed normal, but microscopically it was most abnormal (Fig. 1.). The lobular architecture was still discernible; indeed, there was accentuation of Glisson's capsule by fibrosis and cellular infiltration extending from the portal tracts, but inside this framework the liver cells themselves were so variable in size and shape as to

FIG. 1.—Liver in giant-cell hepatitis (case 1), showing cellular infiltration in the widened portal tracts and thickening of Glisson's capsule outlining the lobules. The parenchymal cells are variable in size and shape and the nuclei of the giant cells stand out as black patches. Hæmatoxylin and eosin, $\times 100$.

be barely recognizable, and there were large numbers of syncytial aggregates forming multinucleated giant cells. I did not relate this at the time to the cerebral hæmorrhage, but events caught up with me, as Dr. Mann will tell you.

DR. MANN: The following year a second child was born in this family and all was well until the age of three months, when she was admitted as an emergency to the Hospital for Sick Children, Great Ormond Street, with the following history. I do not want to waste time and as the story is remarkably similar to the one you have just heard I will give the account in note form:

S. H., full-term normal delivery on 29.9.57. Birth weight 7 lb. 4 oz. Breast fed. No jaundice. Normal neonatal period; indeed, baby perfectly healthy until day of admission, when she developed vomiting, pallor and, seven hours later, stupor, neck rigidity and a bulging fontanelle. Had been vaccinated 11 days prior to the onset of this illness.

On examination she was semi-conscious. Important positive findings: slight right ptosis; right papilloedema and bilateral numerous fresh hæmorrhages; generalized spastic hypertonus with opisthotonus; convulsive movements right arm; some hæmorrhages over the palate. The infant stopped breathing shortly after admission. Right ventricular puncture revealed pure blood at a depth of 1 cm. and blood-stained fluid a little deeper in the ventricle itself. Temporary improvement followed needling, but she quickly collapsed again. Pure blood was then found in the left ventricle. Profuse bleeding occurred from all puncture sites. She died a little later.

DR. ELLIOTT: The autopsy on this patient was performed at Great Ormond Street and the only material I have to show consists of sections of the liver, kindly loaned by Dr. Bodian. The picture is obviously the same in kind as the first case: there is accentuation of Glisson's capsule and the

portal tracts by fibrosis and cellular infiltration, and disorganization of the parenchymal cell pattern with variation in cell size, reduplication of nuclei and syncytial aggregation to form giant cells, though these are fewer in number. The only difference, in fact, is the degree of involvement, which is rather less severe in this case.

DR. BOURNE: Thank you. The object of this exercise is to hear what Professor Sheila Sherlock really thinks.

PROFESSOR SHEILA SHERLOCK (*Professor of Medicine, Royal Free Hospital, London*): My only qualification for being here is that I am a mother, and that gives me the only knowledge of pædiatrics that I have got. Before we discuss these two cases we must clear up two points. The first, is there some underlying cerebral abnormality in these children? And the second, as they both had such severe underlying liver disease, was the bleeding related to hypoprothrombinæmia? So we had better ask Dr. Elliott first whether he is still going to stick by his cavernous change or whether he thinks this is just a straight cerebral hæmorrhage in a child which has liver disease and cannot manufacture prothrombin?

DR. ELLIOTT: I am sure that the cerebral vessels in the first child were abnormal.

PROF. SHERLOCK: Do we know about the second case in Great Ormond Street?

DR. ELLIOTT: There is no mention in the notes from Great Ormond Street of any vascular abnormality of the brain.

PROF. SHERLOCK: We must accept that both these children had liver disease of hepatocellular type. This has led to a deficiency of prothrombin manufacture, which has led to a deficiency in blood clotting. They also had a congenital, cerebral, vascular anomaly and they therefore developed a cerebral hæmorrhage from which they both died. It is surprising that jaundice was not noticed in either of them right until the moment they died, because the underlying liver condition is recognized as so-called 'giant-cell hepatitis' and causes neonatal jaundice (Dible, Hunt, Pugh, Steingold and Wood, 1954). The liver in this condition shows giant cells which consist of syncytial masses with many nuclei in them. There is often a hæmosiderosis, although, as these children were four or five months old, the iron may have disappeared from the liver. Neonates usually show evidence of new blood formation and they also show inflammation. Dr. Elliott, which of these features did you see in the sections?

DR. ELLIOTT: I think that they are all present. The giant cells and the inflammatory infiltration we have mentioned already; there is pigmentation, too. I had written it off as formol pigment, which

is so common in autopsy material, but it could well be hæmosiderin, and some of the areas of cellular infiltration in the portal tracts are probably hæmopoietic rather than inflammatory.

PROF. SHERLOCK: So that, on histological criteria, these two cases would fit into this histological group, which is probably non-specific, and which represents an end-picture of a number of different diseases. So-called 'giant-cell hepatitis' was once believed to be due to virus hepatitis, the agent being of infective type. It was soon plain that this was *not* infective hepatitis, because mothers with hepatitis do not deliver jaundiced babies. If one is faced with an outbreak of hepatitis and one wishes to cut it short, gamma-globulin is given all round and contacts are protected. Mothers pass their own gamma-globulin to their babies and so protect them. So it is most unlikely that this condition is due to the virus of infective hepatitis passing the placenta. For some time it was considered that this condition was due to a carrier state of serum hepatitis and the mother might pass the virus to successive children; this is still possible. This view was put forward originally by Joseph Stokes, of Philadelphia (Stokes, Wolman, Blanchard and Farquhar, 1951). On one occasion he found some volunteers, gave them sera from a mother and from a baby with this condition and the volunteers contracted hepatitis. But this has never been confirmed and attempts at repeating the work have been without success. This, therefore, might be transplacental serum hepatitis, but it is unlikely. There is no doubt but that it is genetic. You may think that involvement of two siblings is an unfortunate coincidence, but the sequence can be duplicated many, many times in the literature. You may feel that it is unwise for such a mother to become pregnant again. Now what genetic advice did you give this mother?

DR. MANN: She has now adopted two children.

PROF. SHERLOCK: Yes, I know of another such family. The mother, a nurse, had two children with cirrhosis; the first died and the second, also cirrhotic, finally developed portal hypertension. This mother has also adopted children. So I think if this misfortune happens in a family it is probably wise to recommend adoption. David Hsia, a geneticist and pædiatrician in Chicago, conducted a family study of a group of siblings of patients with neonatal hepatitis and a group of siblings of patients with atresia of the bile duct. He found that the siblings of cases of neonatal hepatitis showed a statistically significant increased incidence of neonatal hepatitis over the atresia siblings (Hsia, Boggs, Driscoll and Gelliss, 1958). This, of course, makes a virus ætiology more unlikely. The condition of giant-cell hepatitis is a

genetic disease of unknown ætiology which seems to present itself in three different ways: as neonatal jaundice, which these children did not have; as liver failure later, which these children did have; or, thirdly, it may well be the antecedent of later childhood cirrhosis which was seen in these two patients. Now this end-picture is not really an entity, for it may be due to many other liver conditions. For instance, you see it as the type of cirrhosis seen in young women especially, with almost the same histology of the liver except for the hæmosiderosis and hepatic new blood formation; the giant cells are obvious. The same sort of picture is seen with galactosæmia. Dr. Mann, did you consider galactosæmia?

DR. MANN: Well, the answer is no, not at the time, but I have since, and actually two days ago, when we had the summaries for this conference duplicated, I sent them to Dr. Komrower at Manchester and he phoned me up this morning and said that he thought it most unlikely from the data we gave him that they were suffering from galactosæmia. But we certainly did not test their urines at the time.

PROF. SHERLOCK: Why did he say it was unlikely?

DR. MANN: Well, the manner of presentation, the sequence of events, the absence of jaundice and so on.

PROF. SHERLOCK: Was he worried about children not being mentally defective?

DR. MANN: This aspect was not mentioned.

PROF. SHERLOCK: Would you expect galactosæmics to be mentally defective by four or five months, untreated?

DR. MANN: Well, if we say developmentally retarded it could easily be missed at that age.

PROF. SHERLOCK: Too young?

DR. MANN: I think they were a little bit small and, of course, we did not know these children. You see, they were quite unknown to us.

PROF. SHERLOCK: They came in and died very soon?

DR. MANN: Except the first one, who was born at one of our hospitals and was briefly seen two weeks later with umbilical bleeding, which, as I have said, we took to be innocent.

PROF. SHERLOCK: We must keep an open mind about the ætiology, for the same histology in the liver can occur in a number of different conditions. Another is cytomegalic inclusion disease, which is a virus disease, and this agent has been found in the urine from certain children with neonatal hepatitis of giant-cell type (Weller, Macauley, Craig and Wirth, 1957). This is an alternative hypothesis to the genetic one. Now, Dr. Elliott, do you think cytomegalic disease would fit the histology?

DR. ELLIOTT: Well, I would have liked a wider selection of tissues to examine to exclude cytomegalic disease, but I have not found any evidence of it in the material available.

PROF. SHERLOCK: But you would have expected inclusions in the liver cells?

DR. ELLIOTT: Since the liver is so severely affected, yes. I think their absence there makes the diagnosis very unlikely.

PROF. SHERLOCK: Children with neonatal hepatitis usually present much earlier as neonatal jaundice and then they either get better, die of liver failure or go on to cirrhosis. There is very little published about treatment. Some people recommend corticosteroids, but some say these are useless. Do you have any feelings about this, Dr. Mann?

DR. MANN: About steroids? Well, really, I have no experience in this condition.

PROF. SHERLOCK: I suppose if you recognize it, you might as well try corticosteroids, but they may do very little good. These two cases presented rather late for what is usually a neonatal condition. I think this was a neonatal condition throughout, but was not recognized because the child was not jaundiced. If it is recognized in the neonatal period, you have to make the distinction from other causes of neonatal jaundice, especially from biliary atresias, and this is a real problem in neonates. It is very important because if a child has atresia of the bile ducts operation is indicated, whereas if it has got a neonatal giant-cell hepatitis you will probably kill it with surgery. It is almost impossible clinically to make your mind up; they both show the picture of obstructive jaundice. Biochemically the test that offers promise is the serum transaminase. Most of the patients with neonatal hepatitis have very high transaminase values, over 800 units/100 ml., whereas the atresias do not (Kove and Wróblewski, 1960). This estimation is well worth while doing in cases of doubt. The other investigation if you are really in doubt is liver needle biopsy, and I think that paediatricians ought to become much bolder about doing biopsies in neonates (Kaye, Koop, Wagner, Picou and Yakovac, 1959). They can be performed quite easily with a fine Menghini needle (Hong and Schubert, 1960) and this usually will give the answer, although not always. You do see a few giant-cells in the atresias, but not like in hepatitis (Ruebner, 1960). Do you think you could tell the difference on a section, Dr. Elliott, between a biliary atresia and a neonatal hepatitis?

DR. ELLIOTT: I think I would need a little practice.

PROF. SHERLOCK: Well, if you had more biopsies, you would have had the practice. This is *not* academic, because you can easily kill a child with a

neonatal hepatitis by attempting to repair its bile ducts. An enthusiastic surgeon trying to repair a normal bile duct of a patient with a neonatal hepatitis can do a lot of damage. You can see how dreadful these liver cells look; the child will go into liver failure. Finally, if the child has reached the stage of being operated on, I think cholangiography through the gall bladder is essential. As practitioners you are liable to be faced with jaundice as a problem in the neonatal period. Remember, do not rush to have them operated on; remember that you probably will not be able to tell the difference clinically, that it is worth while having transaminase estimations to make sure. If there is any doubt at all, you ought to have a needle biopsy; and if they are operated on, efforts must be made to demonstrate the biliary passages radiologically.

DR. BOURNE: Now, I said that we had a high opinion of Professor Sherlock. I think that you will agree that we are right. And are there any comments?

DR. MANN: Sir, could I ask one question? Our case bled from the umbilicus when it was 14 days old. Should we perhaps have taken this much more seriously? We did not. The baby was only in hospital 48 hours. She appeared healthy and behaved normally during the lying-in period. Perhaps Professor Sherlock will tell us whether we should have done more about this?

PROF. SHERLOCK: Well, you see, I am not a paediatrician. Just how common is umbilical bleeding?

DR. MANN: Well, I would say at that age rather unusual.

PROF. SHERLOCK: Well, I think if it is rare, then you probably ought to have paid more attention to it.

DR. MANN: Yes, I think so.

PROF. SHERLOCK: The umbilicus is a most important clinical focus in the neonatal period. It is of particular interest to me because of its importance in the aetiology of portal vein block in later life (Shaldon and Sherlock, 1962). Umbilical sepsis spreads up the vein to the portal vein, which becomes blocked. The majority of children and young people with a portal vein occlusion have a history of discharge from the umbilicus in the neonatal period. So I think that if bleeding at 48 hours is unusual, then it might have been worth while doing a prothrombin time.

DR. MANN: Thank you very much.

DR. BOURNE: What are the prothrombin times in what you call the neonate?

DR. MANN: Well, in the first week of life they may be quite abnormal: they may be quite prolonged, but you may still get no bleeding at all. But I would have thought that at a fortnight—

I do not know if anyone has done a series at a fortnight—one would expect the prothrombin time to be normal. What would you say, Dr. Nash?

DR. NASH (*Consultant Paediatrician, Brighton and Lewes Hospital Group*): In the middle of the first week it often goes down to 40% of normal in perfectly healthy babies, but a bit lower in those who bleed, and by two weeks it is usually back to normal levels.

DR. MANN: I would just like to ask Professor Sherlock one question if I may, about this technique of needle biopsy which we are persuaded to undertake. Have you any comments as to the actual timing of this procedure? How long should one wait? Obviously one must distinguish, or try to distinguish, between a hepatitis and an atresia—at any rate, an extrahepatic atresia—fairly early on, so that if there is a congenital abnormality to be corrected it is done before there is permanent liver damage. One should, I presume, have to make up one's mind by the age of four to six weeks. Would that be a reasonable sort of timing?

PROF. SHERLOCK: I would not rush. I would wait even two months, because, if the child does have an abnormality of the bile ducts, it will not get irreparable biliary cirrhosis in this time provided surgical relief is possible. Biliary obstruction at whatever the age, if it can be relieved, will rarely cause permanent liver damage. Larger bile ducts than in the neonatal period will be available to work with.

I am sure everybody here is conversant with the dangers of synthetic vitamin K in mothers and neonates in potentiating neonatal jaundice. We might ask the paediatricians: What do you do about vitamin K nowadays? Do you use K_1 , which is supposed to be safe?

DR. MANN: Well, the two of us do different things. Dr. Nash can answer for himself. I personally have never been very keen on vitamin K in any form and I have never been very convinced that it did much good, and so I tend to use it very rarely; that is, prophylactically. If an infant starts to bleed, then I usually give 1 mg. of Synkavit.

PROF. SHERLOCK: That is safe, isn't it?

DR. MANN: I think it is safe in that dosage, but perhaps Dr. Nash would like to comment further.

DR. NASH: Well, we are trying to run a controlled series; controlled after a fashion, that is. Dr. Mann does not use vitamin K very much. I would like to use it routinely in babies who have suffered some anoxic episode or birth damage and even in premature babies, and I do use Konakion, K_1 , not Synkavit. What I really ought to do, I suppose, is to run alternate cases with Synkavit and K_1 , but I think it would take an awful long time to make a comparison.

PROF. SHERLOCK: I am not sure you are justified in using Synkavit. The evidence is that the other one is so much safer. Large doses of vitamin K to mothers and babies make them more jaundiced and potentiate kernicterus in the brain.

DR. MANN: This is particularly in prematures.

PROF. SHERLOCK: Particularly in prematures, as they are going to get jaundiced anyway.

DR. NASH: I think the emphasis is on the level of the dose. I do not think there is any justification for using more than 1 mg. for a full-term baby or 0.5 mg. for a premature baby. The larger doses are being used quite unnecessarily.

DR. BOURNE: When you are doing the liver biopsy, you do it with the baby conscious in the normal way?

PROF. SHERLOCK: Yes, you swathe them top and bottom, hold them down, and put the needle rapidly in and out with perhaps a little local. It is like doing a lumbar puncture; in fact, the size of the Menghini needle is of similar calibre.

DR. BOURNE: How deep do you go? Two centimetres?

PROF. SHERLOCK: You have a guard on your needle so that you cannot go in too deeply.

DR. MANN: You make quite sure that the prothrombin time is normal?

PROF. SHERLOCK: Oh, yes.

DR. BOURNE: You do not have to stop the breathing as you do with adults?

PROF. SHERLOCK: No, I think you can just push on them and just hope for the best. It can be done subcostally. You see, you have got a relatively bigger liver in the baby, so you do not need to worry so much about the breathing.

DR. BOURNE: You do it subcostally?

PROF. SHERLOCK: In babies, usually yes. The safest way of doing liver biopsy nowadays is with the so-called 'one second' method of Menghini. It is very quick and simple, so that it is adaptable for children and babies.

QUESTIONER: Is it just pure coincidence that they were both left frontal haemorrhages?

PROF. SHERLOCK: We will ask Dr. Elliott that.

DR. MANN: It seems a remarkable coincidence.

DR. ELLIOTT: It would be less of a coincidence if a vascular anomaly were present in both, but there is no mention of one in the second case.

DR. BOURNE: Then, I think, perhaps we will go on to the next case, which I think Dr. Mann is going to produce.

DR. MANN: We are now going to present three similar but unusual cases. We shall then look forward to hearing Professor Sherlock's comments upon them.

The first one, J. H., a little boy, was admitted early one morning to the Children's Hospital at the age

18 months with a history of vomiting and irritability commencing the previous day and loud heavy breathing which was noticed during the latter part of the night before admission. It seems likely that the child was comatose for some six hours before being brought to hospital, and certainly the parents were unable to rouse him when they went into him first thing in the morning. There had been no diarrhoea but the buttocks had been excoriated for a few days. Previously his health from birth had been normal.

On examination on admission at 8 a.m. he was comatose, cyanosed and critically ill. His temperature was 98° F. His lips were pale as well as being blue; the tongue was dry. Breathing was irregular and gasping. There was generalized hypotonia. Pupils were small but reacted to light. His fundi were normal. There was no neck rigidity and the anterior fontanelle felt normal. Tendon reflexes were normal and equal on both sides. Bilateral extensor plantar responses were elicited, of doubtful significance in one so young. Other systems normal.

Investigations: Blood sugar on admission—less than 10 mg./100 ml.; same value three hours later after intra-venous and intra-gastric dextrose. Six hours after admission: Blood sugar 295 mg./100 ml.; CSF normal except for low sugar—20 mg./100 ml. Urine: Albumin 150 mg./100 ml., acetone present in large amounts. Haemoglobin: 61%, smear suggested some iron deficiency; white cells appeared normal. Serum electrolytes were as follows: Potassium 5.9 mEq./l., sodium 149 mEq./l., chlorides 116 mEq./l., alkali reserves 15.6 mEq./l., blood urea 62 mg./100 ml. Nose and throat swabs: cultures negative.

Progress and treatment: Oxygen was administered for cyanosis. Shortly after admission he was given 10 c.c. 50% dextrose i.v., followed by 20 c.c. 10% dextrose via intra-gastric tube; thereafter 30 c.c. given hourly. Further i.v. dextrose was necessary three hours after admission for persisting severe hypoglycaemia. Other drugs used were hydrocortisone 100 mg. i.m., streptomycin 250 mg. i.m., paraldehyde 3 c.c. i.m. for convulsions which commenced three hours after admission following the lumbar puncture. The child died three hours later. A terminal blood sample was taken for biochemistry. Serum proteins: Total 4.6 g./100 ml., albumin 3.8 g./100 ml., globulin 0.8 g./100 ml.; A/G ratio 4.7 : 1. Serum alkaline phosphatase 24.2 units; thymol turbidity 1 unit; thymol flocculation 0; zinc sulphate 1 unit; serum glutamic pyruvic transaminase 436 units (normal 22-110 units). Blood urea 87 mg./100 ml.

DR. ELLIOTT: The three cases we are in process of discussing have been grouped together because of close similarities, particularly in the morbid anatomical changes. I will describe the findings in this child fully, and then it will suffice to say simply how the others deviated from this common pattern.

The brain was found closely applied to the skull, with marked flattening of the convolutions, virtual obliteration of the sulci and reduction in amplitude of the pial vessels, producing striking pallor (Fig. 2). This oedema clearly relates to the convulsions during life. Histologically, it was not accompanied by any evidence of inflammatory reaction in the meninges or the brain tissue.

The heart was normal in size and anatomy, but

FIG. 2.—Brain in case 3, showing flattening of the convolutions due to cerebral oedema.

FIG. 3.—Liver in case 3, showing the extreme pallor.

the myocardium was pale and remarkably flabby, so that the left ventricle, laid open, collapsed flat, with no resilience at all. Sections showed cloudy swelling of the myofibrils, but no inflammatory reaction. The lungs were well aerated; there were one or two small foci of haemorrhage in the right lower lobe; sections showed only a little oedema and peribronchial lymphocytic infiltration, nothing to suggest a significant pulmonary infection. The kidneys were large and pale, with cloudy swelling which was confirmed microscopically, otherwise the urogenital system was normal. Spleen and lymph nodes showed active lymphoid tissue, about normal for a child of this age. There was no evidence of any disseminated vascular lesion, Aschoff nodes or focal granulomatous changes.

The stomach was of normal size with a small quantity of tarry mucus in the lumen, but no obvious erosions; the remainder of the intestine was apparently normal; there was no pancreatitis. The liver was enlarged and very pale (Fig. 3), a pallor accentuated after slicing and fixing, due to drainage of blood from the vessels. The specimen I am handing round looks, I think you will agree, as though it was modelled out of soap. Microscopically the pattern was comparatively undisturbed, the portal tracts being of about normal size with little cellular infiltration. In the parenchyma the capillaries were dilated but empty of

FIG. 4.—Liver in case 3. There is no fibrosis and little inflammatory infiltration; the parenchymal cells are uniform in size and uniformly vacuolated. Hæmatoxylin and eosin, $\times 100$.

blood, but the liver cells were normal, and uniform in size (Fig. 4). Some cytoplasmic vacuolation was present, diffusely distributed, but the true state of affairs did not become apparent until frozen sections stained for fat were examined, then it was seen that all the liver cells were uniformly and very heavily loaded with fat. Staining with Nile blue sulphate and examination in polarized light demonstrated that this was almost exclusively neutral fat (Fig. 5).

To summarize, we found cerebral oedema, tarry material in the stomach, and in other organs only the ill-defined qualitative changes which may loosely be described as 'toxic'. The gross fatty change in the liver is the only indication of a possible target organ.

DR. NASH: I would now like to tell you about another patient, who clinically had very similar features to the one just described. This child is the youngest in our series.

M.S., a baby of 7 months, had been ill 3 or 4 days only with what was thought to be an upper respiratory tract infection, and then about 24 hours or so before admission developed an otitis. Shortly after that he lapsed into coma and began to vomit profusely.

On admission he was in deep coma, very ill, and we had a little bit of difficulty in sorting him out, and in fact we did not make a clinical diagnosis at all. I thought at first he probably had a virus encephalitis, but the CSF was quite normal apart from a low sugar (5 mg./100 ml.). Blood sugar was also low, 20 mg./100 ml. Other investigations which were carried out we will not go into in detail except to say that the blood chemistry was quite normal, white cell count normal apart from very slight leucocytosis and a shift to the left. The baby lived in fact for three days. Soon after admission he started convulsing, and then he had laryngeal spasm for which he was intubated, and shortly afterwards, because of the relief obtained, a tracheostomy was done in order to aerate him adequately. He then stopped breathing spontaneously, and he was maintained with the Radcliffe respirator for a matter of 48 hours after that. Perhaps I could just go

FIG. 5.—Liver in case 3, stained for fat. All the parenchymal cells are heavily loaded with fat; there is no sign of any zonal distribution. Frozen section stained with hæmatoxylin and Sudan III, $\times 100$.

back and mention that in the family there had been a history of upper respiratory tract infection in two other children shortly after this child was taken ill. I do not know whether that is of any significance or not. This baby had also had injections. He had had his triphal immunization, one at 4 months, the second at 5 months and the third at 6 months. His mother had had a booster polio injection at six months' pregnancy. I contacted the Public Health Department and discovered that these patients were given their injections with syringes that had been boiled, but recently there has been a switch over to dry sterilization in this area for poliomyelitis vaccination. This child then had the injections with boiled syringes. I do not think there is any more to add—and I am sure we shall hear quite a lot of interest from Professor Sherlock.

DR. ELLIOTT: This child, like the last, showed an oedematous brain; the oedema was less in degree and the pial vessels more prominent, in fact rather congested. The stomach again contained tarry material and there were some small linear excoriations in the mucosa. The liver changes were just as severe; in this case alcohol-fixed material was obtained and I was able to stain for glycogen which proved to be reduced, but present in small amount. Other organs, as before, showed marked 'toxic' changes.

DR. MANN: The third patient is D.K., aged 3 years 9 months, the eldest of the three in this series.

This child was admitted first thing in the morning with a history of nausea and vomiting for 36 hours and seizures commencing the night before she came into hospital. She had had numerous convulsions between 11 p.m. the previous evening and 7 the next morning when she was admitted. There was no history of diarrhoea. The father had vomited a few times when the child had first become sick. *On admission* the child was lightly comatose and could be roused with painful stimuli. She was afebrile though pre-terminally the temperature did go up to 102° F. There was no neck rigidity. Her pupils were equal and reacted to light. Fundal examination showed no papilloedema. All her

reflexes were very brisk and there was bilateral sustained ankle clonus. Her plantar responses were extensor on both sides. There was some injection of both tympanic membranes—in other words a very mild otitis media.

Investigations: Nose and throat swabs negative. Blood culture—no growth after ten days. Microscopy of urine normal. Biochemistry normal except blood sugar 17 mg./100 ml., alkali reserve 36 vol. CO₂% and blood urea 56 mg./100 ml. Hb 99%, w.b.c. 21,600/cu.mm. with a predominant polymorph picture. CSF normal except sugar was slightly reduced at 40 mg./100 ml. Chest X-ray was negative. She was given intravenous dextrose because of her low blood sugar, subcutaneous adrenalin, intramuscular penicillin and streptomycin. Intra-muscular hydrocortisone was prescribed partly because she was critically ill and partly because of her hypoglycaemia. She died 13 hours after admission. Shortly before death Dr. Nash and I were looking at the child together and it occurred to us then that this case was very similar to the two previous ones just described and also to two others we are not presenting tonight, which we saw a year or two ago and on whom a post-mortem diagnosis of 'acute hepatic necrosis', for want of a better term, had been made. This was therefore the tentative clinical diagnosis made here.

DR. ELLIOTT: This brain showed about the same degree of oedema as case 2, and congestion rather than narrowing of the vessels. Tracheostomy had been carried out; there was no abnormality in the upper respiratory tract, but the lungs were oedematous and congested, particularly at the bases, and there were multiple scattered hæmorrhagic patches. There was more tarry material in the stomach than in either of the previous cases, with inflammatory changes in the lower œsophagus, but no gastric erosions. The liver changes were quite as severe as in the other two.

Other organs showed 'toxic' changes, but in this case a curious abnormality was found which I can only describe, as I do not know its significance. In the tubular epithelium, in the medulla, was a dusting of brown pigment, present as fine granules or in the form of tiny annuli, somewhat reminiscent of malaria parasites. The distribution varied from tubule to tubule, but was fairly consistent in any given tubule, all the cells being affected to about the same degree. This material gave a faintly positive reaction to Perl's reagent for ferric iron and von Kossa's method for calcium; it was also slightly birefringent. Re-examination of other tissues showed that similar, but fewer, granules were present in the lungs, and in the liver parenchymal cells, but only in the subcapsular zone, which is rather suggestive of a fixation artefact. No trace of any material resembling this was found in the two other cases.

DR. BOURNE: Well, I am quite sure that hidden away at the back of Professor Sherlock's brain

there are a number of facts which are quite relevant and I will ask her to produce them.

PROF. SHERLOCK: Well, these are three extremely interesting patients. The salient features of all three were vomiting, convulsions, coma and a low blood sugar. So you ask, what would do that? The first thing I thought of, before I saw the histology of the liver, was that the children were poisoned. The second was that they had something wrong with the brain, such as a meningitis, encephalitis or hæmorrhage into a tumour. The third was that they had a severe infection with perhaps adrenal hæmorrhage. The final suggestion would be liver failure, due to fulminant hepatitis. Now let me say right away that this is not the histology of fulminant virus hepatitis, for fat is never prominent in such livers. Is this a reasonable differential diagnosis?

DR. MANN: I think it is very reasonable.

PROF. SHERLOCK: Which of these can we exclude? Well, the cerebral ones are excluded straight away not only from post-mortem, but ante-mortem, for the clinical picture was not that of meningitis, encephalitis, nor of primary cerebral disease. Would the degree of cerebral oedema we saw as an isolated lesion kill a child?

DR. MANN: I would have thought probably no.

PROF. SHERLOCK: So that we are left with poisoning, severe infections, adrenal hæmorrhages (which they have not got) or pure liver failure. Very severe fatty change in the liver is not necessarily fatal. For instance, babies suffering from the tropical condition of kwashiorkor have their livers absolutely stuffed with fat, yet can recover perfectly. So it is difficult to believe that the fatty change killed these children. Now, why would they have this severe fatty change? The fat had to come from the depots. So were these very well nourished children who had obviously got thinner rapidly? Dr. Elliott, how often do you see this degree of fatty change in children dying?

DR. ELLIOTT: I would say I have not seen it, not as severe as this.

PROF. SHERLOCK: But it is common in children to get a moderate degree of fatty change?

DR. ELLIOTT: Yes, a moderate degree certainly.

PROF. SHERLOCK: Were they well-nourished children?

DR. MANN: They were not weighed, of course, but they were quite normal-looking children. Now, I remember one was very fat indeed.

DR. ELLIOTT: Case 2 was the fattest baby I have ever seen.

PROF. SHERLOCK: I am glad to hear you say this, because fat babies get fat livers and get them more easily. This is true of all ages—the fatter you are, the fatter your liver. The liver was perhaps unable to metabolize fat from depots,

perhaps because it was 'toxic'. I was surprised that all three children received paraldehyde, because if you are expecting liver dysfunction this should never be given. It is a most dangerous drug for anyone on their way towards hepatic coma; in fact, although almost any drug is bad, paraldehyde is about the worst, because there is no antidote. Now, why do you go on using paraldehyde?

DR. MANN: Well, I think the answer to that is that it is *the* most effective anticonvulsant drug. Children do die of convulsions and, of course, when we gave it we did not suspect there was anything wrong with their livers; in fact, it was only in the third case, preterminally, that we did think of a liver disturbance at all.

PROF. SHERLOCK: Yes, but if there is any question of the liver being involved, you might be better with phenobarbitone, which is excreted mainly by the kidney. Do you know if convulsing children do as well with phenobarbitone?

DR. MANN: On the whole, most disappointing.

PROF. SHERLOCK: Well, I suppose you have to weigh the danger of them dying of the convulsions against the danger of them getting worse from the liver coma. If you ever give paraldehyde to anyone with cirrhosis, you will smell it for a week. It is a really noxious drug for hepatic patients and I am surprised that with all the newer anticonvulsants available you still have to use paraldehyde.

DR. MANN: We very often try the others, but when all fails we usually finish up by giving paraldehyde.

PROF. SHERLOCK: We have left the question of whether these children could have been poisoned—if so, with what—or whether they could have had a severe infection. I think they were given or took something noxious. Certain herbs are poisonous. What sort of lives did these children lead? Were they in the country? Did they chew berries?

DR. MANN: Can I answer this one? As regards my first case, J.H., I should have mentioned that we went into this question of poisoning very carefully indeed. The mother assured us that there was no possibility of the baby having taken any poisons or drugs. There were no sleeping tablets in the house.

PROF. SHERLOCK: Fatty livers are a bit unusual, except in cases of obesity, malnutrition, infection or poisoning. So I would bet one of these children had taken something or that they had some sort of overwhelming infection. Now in one of them we were sure that the intestine was normal, but could not they, in fact, have had some sort of infection that you have not identified? I am unwilling to accept these as hepatic deaths.

DR. ELLIOTT: Infection is always a difficult thing to exclude. One child had a history of otitis;

the middle ears were examined and a culture taken, which produced *B. coli*. This is such a common contaminant in post-mortem cultures that one tends to disregard it. Macroscopically, the lungs in case 3 might have been infected, but the sections did not support this. All three cases showed fatty mucus in the stomach, with erosions in two; this makes gastroenteritis a possibility, but it is a difficult diagnosis to make post-mortem. I had a case of gastroenteritis a few days ago and sections do not show anything dramatic.

PROF. SHERLOCK: What did the liver look like in your case of gastroenteritis?

DR. ELLIOTT: There was some fat, but nothing like the amount present in these cases. The kidneys showed no sign of infection. That leaves the possibility of a virus infection. On the assumption that this condition was most likely to be a fulminant virus hepatitis, the possibility of culture was not considered, but, of course, some other virus could be responsible and we will look into this if the occasion occurs again.

DR. NASH: Perhaps I could add to that: that in the middle case, the one I saw, we did, in fact, keep some serum and CSF in deep freeze. We really got nothing out of it. Tissue cell culture and inoculation were negative; if it had been positive, it would have been nice, but it does not really help us.

DR. MANN: What sort of infection could we be dealing with here? We see a great deal of gastroenteritis in Sussex and have a very active unit for these cases, but I must say that in neither of my cases did the possibility of a bowel infection even cross our minds.

May I ask Professor Sherlock what investigation she would advise the next time we see a child with this sort of affection? I am quite sure we are going to see more of these cases and, furthermore, I think we may now be able to recognize the syndrome clinically.

PROF. SHERLOCK: I should get a toxicologist to see whether a hypoglycaemic agent is circulating. Admittedly hypoglycaemia is commoner in childhood than it is in adults, but it is unusual in liver disease. I think you ought to continue your virus studies. You have really got nothing in these livers except fatty infiltration. There is no evidence of an infection, is there?

DR. ELLIOTT: No none at all, and no necrosis either.

DR. MANN: What about liver function tests? Is it worth doing these, do you think?

PROF. SHERLOCK: You will probably find high serum transaminases, but this will not get you any further. In treatment the most important thing is not to give them paraldehyde; to give them large amounts of glucose and vitamin K

and watch their electrolyte balance. I doubt whether steroids will be helpful; in fact, they were not, were they?

Comment from audience: These three children all became ill in the winter time, so that poisoning with berries is surely unlikely.

QUESTIONER: Could these children have had something wrong with the alpha cells of the pancreas?

DR. ELLIOTT: The pancreas undergoes rapid autolysis after death. I do not think I could say.

PROF. SHERLOCK: Well, it is a very good point. The child could have taken an alloxan-like substance which might have damaged the pancreas, so it might be worth while taking a closer look at the pancreas in other cases.

DR. ELLIOTT: Well, I will certainly try. But the youngest of these children was only seven months old. He could not on his own account have eaten anything unusual, could he?

PROF. SHERLOCK: I do not think this is one entity. You might reach this end result of diffuse fatty change in the liver by a number of different paths and I do not think these three children are necessarily suffering all from the same condition.

DR. MANN: The clinical picture is remarkably constant.

PROF. SHERLOCK: Yes, but the clinical picture of respiratory failure is remarkably constant, and so is the picture of liver failure, whatever the cause.

DR. MANN: Is the vomiting a feature you would expect?

PROF. SHERLOCK: When children die in liver failure they vomit. Very severe, acute virus hepatitis in childhood, for instance, is characterized by vomiting.

DR. NASH: Would you say the central nervous signs, apart from vomiting, give a picture of liver failure? The patient I showed undoubtedly had a stiffness of limbs. I doubt whether that was due to the hypoglycæmia which was corrected within a matter of hours of admission.

PROF. SHERLOCK: Almost any neuropsychiatric disturbance is seen in liver failure in childhood. In general, liver failure in childhood is much more acute than it is in adults, usually with an acute organic mental reaction with convulsions, screaming, mania and then coma. An adult patient with cirrhosis goes into coma gradually, but a child will do it very quickly indeed, giving a quite different picture. I remember such a patient in one of the London children's hospitals: the screaming could be heard from the end of the road as you approached the hospital. This is the type of reaction seen in fulminant liver failure in childhood. Convulsions are very common. The typical flapping tremor, found in adults, is very rarely elicited in childhood. Again, as in these three

children, there may be no jaundice. Vomiting is one of the major signs and a shrinking liver, of course, has a very bad prognosis in hepatitis. The picture of liver failure in childhood rather resembles the effect of hepatectomy in an animal; the animal convulses, gets hypoglycæmic and dies, and this is quite different from the so-called protein intolerance in adults. But I am still doubtful whether these three children were, in fact, in liver failure, because I do not think the hepatic histology is compatible. I do not think an uncomplicated fatty liver will fail.

DR. BOURNE: Does anyone want to ask any questions or make any statements or throw any light?

QUESTIONER: I thought I understood Dr. Elliott to say that the last child was so young that it could not have taken anything on its own, but then it could have been given berries by another youngster. Also, what about fruit and vegetables which have been treated with insecticide?

DR. ELLIOTT: I have seen a number of cases like this over the years and I have always called them acute hepatic necrosis. Professor Sherlock has convinced me that this is not an appropriate diagnosis, but it is one that I have been using for a long time. The first case I saw was in 1944, when organic insecticides were not in common use. I do not think that the condition has become more frequent in recent years now that they are used extensively.

QUESTIONER: Baby S., the third case, had laryngeal obstruction. Can you comment on that?

DR. NASH: Well, he also had quite marked spasticity of his arms and, to a lesser degree, of his legs. I thought he had laryngospasm; in other words, I believed the obstruction was neurogenic in origin.

QUESTIONER: Is there an explanation for the polymorphonuclear leucocytosis? About 21,000 I think it was in one case?

DR. MANN: All we found clinically in that case was a very mild otitis media, such a common finding in children. I think the answer is no.

DR. NASH: One does get it sometimes after convulsions in children and when patients become acidotic; diabetic coma, for instance. I think Dr. Mann's patient did have a low blood bicarbonate?

DR. MANN: Yes, 36 vols. CO_2 %.

DR. BOURNE: I think we really must make sure Professor Sherlock catches her train back to London. I am quite sure you all want to thank her very much indeed.

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