similar to those resulting from exposure to high oxygen concentrations. They tentatively suggested that the mechanism at work was one of inhibition of glycolysis resulting in swelling of retinal tissue and subsequent vascular compression and obliteration (see also Graymore, 1958). By this technique they were able to produce a biochemical lesion owing to a particular vulnerability linked to a definite stage of functional development and maturation, and it is worth noting that similar changes could not be produced by them in the eyes of more adult cats. If the incidence of cerebral palsy (particularly cerebral spastic paraplegia/diplegia) were greater in babies stressed by high oxygen concentrations, the hyperoxic hypothesis would perhaps be more acceptable. Fuldner (1955) found an association between cerebral spastic paraplegia and retrolental fibroplasia. That the incidence of cerebral spastic paraplegia/diplegia in babies with retrolental fibroplasia is greater than would be expected has been shown by Ingram and Kerr (1954). However, they suggested that the cause of cerebral damage in their patients was abnormality of pregnancy and of labour, leading to post-natal asphyxia which necessitated oxygen therapy and in turn caused retrolental fibroplasia.

The above suggestion that premature birth may at times cause post-natal interference in development and maturation of critically maturing neurones is entirely hypothetical. It can be put to the test by experiments with high oxygen pressures in immature animals. The understanding of the delicate metabolic mechanisms involved can be furthered by detailed studies of the vascular, enzymic, histological, and functional maturation of the human brain, in continuation of the work done by Racker (1942) and Viliee (1953). The main use of such a hypothesis is that it directs attention to possibilities of prevention.

Summary

The incidence of prematurity in various clinical types of cerebral palsy is reviewed. A particularly strong association is found with two neurological syndromes: dystonic/choreo-athetoid cerebral palsy following severe neonatal jaundice not due to blood-group incompatibility, and cerebral spastic paraplegia/diplegia. The possible mechanisms of this latter relationship are considered and a selective developmental origin for the neurological troubles is favoured tentatively. Because of the association between retrolental fibroplasia and cerebral spastic paraplegia/diplegia, and because of the clinical features of the cerebral spastic paraplegia syndrome without history of perinatal or postnatal troubles, a postnatal interference with development is the mechanism postulated for this clinical type of cerebral palsy.

The terminology on cerebral palsy used in this paper is based on the discussions of a group of workers interested in the subject at meetings of the Little Club. The help of those concerned is gratefully acknowledged.

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CORTICOTROPHIN AND STEROIDS IN THE DIAGNOSIS AND MANAGEMENT OF "OBSTRUCTIVE" JAUNDICE

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Jaundice due to hepatitis with prolonged bile retention (Eppinger, 1937; Watson and Hoffbauer, 1946) or occurring as a complication of therapy with chlorpromazine and other drugs (Hanger and Gutman, 1940; Hollister, 1957) may have clinical and biochemical features indistinguishable from that associated with extrahepatic biliary obstruction. Solem and Olsen (1953), aware that jaundice in patients with hepatitis often clears rapidly with steroid therapy (Ducci and Motlis, 1951), reported that the effect of a four to seven-day trial of corticotrophin (A.C.T.H.) therapy on the icteric index permitted a clear-cut distinction between extrahepatic obstructive jaundice, which was not significantly influenced, and hepatitis. However, later observations showed that the effect of corticotrophin or steroids in hepatitis was very variable (Sborov *et al.*, 1954) and that considerable reduction in serum bilirubin concentrations could follow use of the drugs in extrahepatic biliary obstruction, thus invalidating their application as a diagnostic test (Chalmers *et al.*, 1956; Katz *et al.*, 1957).

The subject has received only passing mention in this country (Shaldon and Sherlock, 1957; Summerskill, 1958), although the laparotomy indicated in extrahepatic obstruction may be unnecessary and hazardous in hepatitis. We therefore report the effect of corticotrophin and steroid drugs on serum bilirubin and alkaline

phosphatase levels in relation to ultimate diagnosis when applied exclusively to patients with "obstructive" jaundice of uncertain cause.

Material and Methods

Four male and eight female patients aged between 26 and 74 years (average 56) were studied (see Table). The clinical and biochemical findings consisted essentially of progressive jaundice, itching, and hepatomegaly, without fever, sudden prior deterioration in general health, or significant aetiological precedents. These were almost invariably associated with very high serum alkaline phosphatase levels; negative thymol turbidity and flocculation tests; the absence of occult blood or bile pigment from the stool and urobilinogen from the urine; and no relevant radiological abnormality on plain x-ray examination of the abdomen or by barium meal.

Five patients (Cases 1-5) had hepatitis, six (Cases 6-11) had extrahepatic biliary obstruction due to carcinoma later demonstrated at laparotomy, and an ampullary carcinoma was finally shown radiologically in one (Case 12). Jaundice had been present for periods of two weeks to three months and was accompanied by itching except in two cases (Nos. 6 and 7) with carcinoma. Case 3 had had a blood transfusion four months before the onset of jaundice, and a tooth was extracted three months previously in Case 5, but none gave a history of contact with hepatitis, recent injections, or drug consumption. Two patients (Cases 3 and 9) complained of vague prodromal symptoms, and one patient with hepatitis (Case 2) had had a cholecystectomy for gall-stones. One patient (Case 9) who had an operable ampullary carcinoma had profuse vascular "spiders," but none of the other patients showed cutaneous stigmata suggestive of liver-cell disease.

The serum bilirubin concentration was above 10 mg./100 ml. in all patients. The serum alkaline phosphatase level was elevated in all except Case 2, and the value was above 30 King-Armstrong units (normal <12 units) at the same stage in 10 patients. Flocculation tests were positive intermittently in Case 4 and negative in the remainder.

Serum bilirubin was estimated by a modification of the method of van den Bergh (1918), and serum alkaline phosphatase was measured by the method of King and

Armstrong (1934). Corticotrophin or steroid drugs were given after at least two preliminary biochemical studies had been made during a control period of five or more days. The drugs were then given daily for five to eight days, after which time the biochemical investigations were repeated. In five patients longer courses of the drugs were given with continued biochemical control. Six patients received oral prednisone (60-50 mg. daily), five were given corticotrophin (60 units daily) by injection, two had oral cortisone (300-200 mg. daily), and one was treated with triamcinolone ("ledercort"; 9- α -fluoro-16- α -hydroxyprednisolone),

FIG. 1.—Effect of corticotrophin and steroids on serum bilirubin concentrations in hepatitis with obstructive features.

12 mg. daily. The drugs were used on 14 occasions, as two patients each had separate trials of corticotrophin and a steroid preparation.

Results

Four of the five patients with hepatitis (Cases 2-5) showed a rapid and profound improvement in jaundice in response to corticotrophin or steroids after serum bilirubin levels had been unchanged or climbing in the control periods. Treatment was continued in Cases 2 and 3, with progressive clearing of the jaundice, whereas the biochemical improvement was slower in Cases 4 and 5, in which only short courses of the drugs were given (Fig. 1). The fall in serum bilirubin concentrations in these patients was between 8

Case Material and Response to Treatment with Corticotrophin and Steroids

Case No.	Sex and Age	Diagnosis	Duration of Jaundice Before Test	Drug and Duration	Serum Bilirubin (mg./100 ml.)			Serum Alkaline Phosphatase (K.A. Units)		
					Before	After	Change per Day	Before	After	Change per Day
1*†	F 64	Hepatitis { (1) (2)	6 weeks	Corticotrophin 60 u. daily × 5	17.5	16.0	-2%	31.5	18.5	-8%
2*	F 56	"	18 "	Triamcinolone 12 mg. daily × 7	25.0	16.0	-5%	88.5	73.0	-2%
3*	M 63	"	4 "	Prednisone 60 mg. daily × 8	17.5	4.0	-9%	12.0	13.1	+1%
4	F 48	"	4 "	Cortisone 300 mg. daily × 7	18.0	6.0	-10%	28.5	22.0	-3%
5	F 26	"	5 "	Prednisone 40 mg. daily × 4	23.5	15.5	-8%	—	—	—
			4 "	Corticotrophin 60 u. daily × 4	12.8	6.4	-12%	40.0	28.0	-7%
				Mean	19.0	10.6	-8%	40.1	30.9	-4%
6	F 56	Ampullary carcinoma	2 weeks	Corticotrophin 60 u. daily × 5	12.5	10.0	-4%	57.0	45.5	-4%
7*	F 58	"	5 "	Prednisone 60 mg. daily × 5	11.0	15.0	+7%	—	—	—
8	F 52	Carcinoma of gall-bladder and bile ducts	3 "	Corticotrophin 60 u. daily × 5	16.0	10.0	-7%	28.0	24.0	-3%
9	M 52	Carcinoma of common bile duct { (1) (2)	2 "	Corticotrophin 60 u. daily × 7	15.0	9.0	-6%	63.0	20.5	-10%
10	F 74	"	4 "	Prednisone 60 mg. daily × 7	24.0	12.5	-7%	21.8	16.1	-4%
11	M 63	Ampullary carcinoma	4 "	Prednisone 60 mg. daily × 5	20.0	25.0	+5%	67.5	62.5	-1%
12	M 63	"	3 "	Prednisone 50 mg. daily × 5	18.0	15.0	-3%	57.3	68.0	+4%
		Ampullary carcinoma and portal cirrhosis (inactive)	3 months	Cortisone 200 mg. daily × 5	15.0	16.0	+1%	74.0	79.5	+1%
				Mean	16.4	14.0	-2%	51.2	45.1	-2%

* Patients receiving longer courses of drug in addition (see Figs. 1 and 2).

† Presumed to have hepatitis on the basis of a negative laparotomy and surgical cholangiography. However, nine months later, jaundice and itching continues and the possibility of a bile-duct carcinoma becomes increasingly likely.

and 12% a day (see Table). The other patient (Case 1) failed to respond to corticotrophin and had a less impressive reaction, which was not sustained, with steroid therapy (Fig. 1).

There was a slight decrease (Cases 6 and 11) or negligible increase (Cases 7, 10 and 11) in serum bilirubin levels in five patients with extrahepatic obstruction during the administration of corticotrophin or steroids. Case 8 showed a fall equivalent to 7% a day, but the level was declining in the control period and failed to rise after corticotrophin was stopped. Case 9 had particularly convincing responses to

FIG. 2.—Effect of corticotrophin and steroids on serum bilirubin concentration in extrahepatic obstructive jaundice.

both corticotrophin (a fall of 6% a day) and prednisone (a fall of 7% a day), as there were sharp returns of the serum bilirubin concentration up to control levels as soon as the drugs were stopped (Fig. 2).

Changes in serum alkaline phosphatase concentrations were usually similar to those in the serum bilirubin levels, although less striking in degree (see Table). The level tended to fall during treatment in patients with hepatitis and extrahepatic obstruction but to a greater extent in the former group. Changes in serum bilirubin and alkaline phosphatase levels were occasionally disproportionate (Cases 1, 2, 10, and 11).

No apparent difference in response of the serum bilirubin and alkaline phosphatase levels was found in relation to the drug used (see Table) or to the doses prescribed. When a response occurred it took place immediately, and the duration of drug administration for longer than a period of four to five days was of importance only as a therapeutic measure in patients with hepatitis (Figs. 1 and 2).

Apart from fluid retention in Case 9 during corticotrophin administration, no toxic effect resulted from diagnostic use of the drugs. Case 1, however, had mental changes during the long-term administration of prednisone, and later, when still jaundiced, developed a duodenal ulcer while receiving triamcinolone.

Liver biopsy was performed for diagnostic purposes in four patients. Histological appearances of obstruction were found on three occasions, and these were non-specific in Cases 1 and 9, although the additional features of inflammatory cell infiltration of the lobules suggested hepatitis in Case 2. In Case 12, portal cirrhosis was found, without definite evidence of biliary obstruction, although it was subsequently proved that jaundice was due to obstruction from an ampullary carcinoma.

Discussion

These findings accord with earlier observations that corticotrophin and steroid compounds may influence the jaundice both of hepatitis and of extrahepatic obstruction, but they challenge the conclusion (Chalmers *et al.*, 1956) that the drugs have no application for the purpose of differential diagnosis between the two conditions. Four of five patients with intrahepatic obstructive jaundice due to hepatitis had reductions in serum bilirubin levels which exceeded any that occurred in patients with extrahepatic obstruction due to tumour. The "critical" figure in this series was a fall in the serum bilirubin level of 8% or more a day in a period of four to eight days, and review of earlier studies in patients with extrahepatic biliary obstruction shows that such a response to corticotrophin is very rare indeed in such cases (Chalmers *et al.*, 1956; Katz *et al.*, 1957). However, the practical importance of the procedure is the continued administration of the drugs to those who have shown some definite response to the initial test, as sustained improvement permits a confident diagnosis of hepatitis. Corticotrophin or steroid therapy is the treatment of choice for such patients (Johnson and Doenges, 1956), although histological improvement lags behind apparent clinical and biochemical recovery (Shalden and Sherlock, 1957).

Failure to improve with treatment does not exclude hepatitis, and the variable response of patients with hepatitis to corticotrophin or steroids is unexplained. In virus hepatitis, a proportion of patients may present with variable clinical, biochemical, or histological features of obstruction, and these sometimes dominate the picture. Six patients with such "cholangiolitic" findings responded to corticotrophin very much better than the remainder of 49 cases of hepatitis treated by Sborov *et al.* (1954); and Johnson and Doenges (1956) also commented on the prompt improvement after corticotrophin in two cases of hepatitis with obstructive features.

This susceptibility of patients with hepatitis and intrahepatic bile retention to respond to corticotrophin probably explains the success of corticotrophin and steroids as a diagnostic test for obstructive jaundice in this series, in contrast to the overlap in effect reported by Chalmers *et al.* (1956) when patients with "classical" hepatitis were compared with those with extrahepatic obstruction. Certain drugs, notably chlorpromazine, may produce identical features of prolonged intrahepatic bile retention, but this will be evident on direct questioning of the patient or his practitioner. Reports of the effect of corticotrophin or steroids on the jaundice of such cases are conflicting (Hollister, 1957), and insufficient data are at present available. In addition, it is likely that other agents, at present unrecognized, may produce the syndrome of intrahepatic bile retention, and in only two of the five patients reported here could any accepted aetiological factor be incriminated. The poor response to steroids and the atypical nine months course in Case 1 could be explained on this basis.

The mode of action of corticotrophin and steroids in lowering serum bilirubin concentrations in some patients with extrahepatic obstructive jaundice is uncertain. The original conception of a choleric action (Patterson *et al.*, 1954) would seem to be invalidated by the observation that prednisone or cortisone causes no increase in faecal urobilinogen and bilirubin, despite reduction of serum and urinary bilirubin levels (Katz *et al.*, 1957). Occasionally, as could have happened in Case 8, treatment may coincide with spontaneous improvement in jaundice and the degree of

bilirubin excretion. The decreases in serum bilirubin concentrations during treatment in Case 9 cannot be attributed to this, and delay in red cell or haemoglobin breakdown due to steroids (Katz *et al.*, 1957) seems unlikely to explain such great reductions. Alternatively, deviation of haemoglobin metabolism to compounds which do not react with the diazo reagent, or increased storage of bilirubin in the reticulo-endothelial system and other tissues, might be responsible, but the coincident decreases in this study in serum levels of alkaline phosphatase, which is thought to be eliminated mainly in the bile, are more compatible with increased excretory activity.

The usefulness of corticotrophin and steroids in distinguishing between intrahepatic and extrahepatic jaundice has encouraged us to incorporate the test in the routine investigation of obstructive jaundice of uncertain cause. After two weeks, in which time standard investigations (stool occult blood, haematology, barium meal, liver-function tests) have been done, a five-day trial of corticotrophin or steroids on the serum bilirubin level is performed if the diagnosis remains in doubt. Oral prednisone (20 mg. t.d.s.) may be the drug of choice. It reaches the liver direct in portal blood, and corticotrophin has the disadvantage of variable potency due to batch differences. An apparent response to this measure is followed by continued treatment. In patients who fail to respond and in whom there is no haematological contraindication, liver biopsy can be performed with less hazard than laparotomy in the jaundiced patient, and its interpretation in obstructive jaundice was well reviewed by Johnson and Doenges (1956).

Unfortunately, cases which are equivocal from clinical and biochemical standpoints often have non-specific histological findings. However, dilatation of large intrahepatic bile ducts and bile extravasation suggest extrahepatic obstruction, while, as in Case 2, evidence of liver-cell damage and cellular infiltration indicates hepatitis. In addition, cirrhosis or another unsuspected lesion may be demonstrated, as in Case 12. If the diagnosis is still in doubt, laparotomy with arrangements for cholangiography must be considered to resolve the doubts of both doctor and patient. Obstructive jaundice is not harmful (Atkinson *et al.*, 1956), and it is reasonable to wait eight weeks for possible improvement, as operation is poorly tolerated by patients with hepatitis (Sherlock *et al.*, 1954). Sometimes, as in Case 1 (who was jaundiced for nine months), laparotomy appears inevitable in a patient subsequently shown to have hepatitis, but the relative absence of liver-cell damage on clinical, biochemical, and histological investigation probably allows these patients to withstand operation better than others with hepatitis.

Summary

In 12 patients with obstructive jaundice of uncertain cause, the effect of a five-day trial of steroid or corticotrophin therapy was of great value in reducing serum bilirubin levels and in differentiating between intrahepatic obstruction due to hepatitis and extrahepatic obstruction. Serum alkaline phosphatase concentrations also fell during treatment, although to a less extent, thus suggesting that the reduction of jaundice caused by corticotrophin or steroid drugs was due to increased bile excretion. The drugs acted immediately and no difference was apparent between corticotrophin and steroids.

The place of these drugs and other measures in the diagnosis and management of obstructive jaundice is discussed.

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THROMBOCYTOPENIC PURPURA DUE TO QUINIDINE

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The fundamental observations on drug-induced thrombocytopenia were made by Ackroyd (1949a, 1949b, 1951, 1954) in his classical work on "sedormid" purpura. He showed that the drug caused agglutination and lysis of the patient's platelets *in vitro*, and that the addition of the drug to the patient's blood *in vitro* inhibited clot retraction.

We describe below a simple method for showing platelet agglutination. This method enables the investigator to obtain suspensions of platelets which have no tendency to spontaneous clumping. Stress is laid on the clinical features of quinidine purpura and the practical conclusions to be drawn from them.

Case Report

On December 31, 1957, a man aged 50 was admitted to Hadassah Hospital because of haematuria and purpura. He looked seriously ill. There were widespread petechiae, and blood-filled blisters were seen in the mouth and on the tongue. The urine had the appearance of blood. The blood pressure was 170/100. The blood count showed haemoglobin, 69%; erythrocytes, 3,500,000; leucocytes, 10,000 (neutrophils 59%, eosinophils 2%, monocytes 2%, lymphocytes, 37%). No platelets were seen; bleeding-time was 2 minutes; coagulation time 2 minutes, and prothrombin 58%. The urine showed many red cells. The tourniquet test was strongly positive. Prednisone, 60 mg. a day, was given. By his fourth day in hospital the urine was clear, the platelet count had risen to 25,000, and he was feeling much better. By the seventh day the platelets had risen to 100,000; two days later they numbered 240,000.

A detailed history revealed that the patient had had a myocardial infarction two years previously. In July, 1957, he was given quinidine because of palpitations; he took four 0.2 g. tablets. A month later he took another tablet. Two days before admission he felt palpitations and took two tablets, one at midday and one in the evening (0.4 g.). That night he had a severe rigor and his temperature rose to 39° C. (102.2° F.). Next day he felt weak and noticed a rash on his hands. On the following day blood appeared in his urine and he was sent to hospital. He had taken 1.4 g. of quinidine at intervals, over a period of six months.