level of proteins of extrahepatic origin—that is, γ -globulins. Viewed in this light the customary facile explanation of “a compensatory increase” of globulin contains some sense.

Summary

Electrophoresis of serum proteins in 38 cases of ascites revealed distinct and constant patterns in the major groups with hepatic fibrosis or carcinomatosis peritonei. Other conditions, which form a minority of cases, produce less characteristic changes.

The pathological processes underlying these changes are discussed, and the diagnostic value of serum electrophoresis in this context is assessed.

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MULTIPLE VISCERAL LESIONS DUE TO PHENYLBUTAZONE TOXICITY

BY

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During the past year many reports have appeared stressing the toxic effects of phenylbutazone. Among the most important of these effects have been agranulocytosis, reactivation of peptic ulcer, jaundice, renal lesions, skin rashes, and oedema (Kuzell *et al.*, 1952; Cudkowicz and Jacobs, 1953; Etes and Jacobson, 1953; Stifel and Burnheimer, 1953).

We have recently seen a patient in whom the drug caused multiple visceral lesions and posed problems in differential diagnosis.

Case Report

A 53-year-old woman attended another hospital in January, 1953, because of severe pain in the right hip due to osteoarthritis. Treatment with analgesics and physiotherapy gave no relief. In April she was admitted to hospital, where she derived some benefit from femoral traction. However, soon after discharge the pain increased and she was given phenylbutazone, 200 mg. thrice daily. A few days later she developed diarrhoea, diagnosed by her own doctor as gastro-enteritis, and treated with kaolin mixture; phenylbutazone was stopped. After the diarrhoea had ceased the patient again took the drug, as it had given

her great symptomatic relief. Within a few days she noticed increasing swelling of her feet and legs, and, soon after this, complained of anorexia, headache, pains in the limbs, substernal pain, and fever. Phenylbutazone was again stopped, but her fever and general condition did not improve. On readmission to hospital on June 11, 1953, she was found to be very ill. Her temperature fluctuated between 99 and 101° F. (37.2 and 38.3° C.), the conjunctivae were suffused, a slight erythematous rash was present on forehead and chest, and there was a maculo-papular rash on both shins: the legs were moderately oedematous and the blood pressure was 100/70. There was slight anaemia (Hb 67%) and a sedimentation rate of 65 mm./hr., but the white blood count was repeatedly normal. The urine contained albumin, a trace of bile pigment, a marked excess of urobilinogen, and granular casts. A tentative diagnosis of leptospirosis was made at this stage, but repeated agglutination tests remained negative. On re-testing the urine ten days later, it was found to contain large quantities of sugar, and a glucose-tolerance test showed a typical diabetic curve; serum amylase levels were repeatedly normal. She was given 12 units of globin insulin daily until the glycosuria had disappeared 10 days later.

An E.C.G. taken on June 23 because of the chest pain showed: “Sinus rhythm 60/min.; horizontal heart; T waves low in AVL, I, and inverted in V₃₋₆, consistent with non-specific myocardial changes.” Radiographs of the chest remained normal. Repeated liver function tests showed a reversed A/G ratio (3.4 g./4.5 g.), rising thymol turbidity, and positive flocculation reactions.

The diagnosis now seemed to be between viral hepatitis and phenylbutazone poisoning. A liver biopsy (see Fig.) was therefore taken, on which Professor Crawford reported: “Sections show a moderate degree of fat accumulation in the liver cells. Individual cells contain large droplets of fat, and the affected cells are irregularly distributed without any special lobular arrangement. There are numerous foci of focal necrosis into which infiltration with mononuclear cells has occurred, and there is also some accumulation of mononuclear cells in the portal tracts. These appearances suggest toxic damage to the liver, and are consistent with the suggestion that the lesion is due to phenylbutazone.” This finding led to the final diagnosis of poisoning with phenylbutazone.

During the second week in hospital the patient's condition improved: the fever subsided and she lost her

Liver biopsy, showing area of focal necrosis with round-cell infiltration. (H. and E. $\times 200$.)

symptoms. At the time of discharge, eight weeks after admission, the glucose-tolerance test was still slightly abnormal and the thymol turbidity appeared to be rising; all other abnormal findings had reverted to normal. Further assessment on September 27 showed her to be in excellent health, but the thymol turbidity had risen further to 7.3 units and her tolerance to glucose was still decreased. In the E.C.G., recovery of the T waves began to take place by July 13, and there was a return to a picture within physiological limits by September 7: "T waves are a little low in V_{5-6} , but within physiological limits."

A follow-up on January 18, 1954, showed normal liver function and glucose-tolerance tests; the urine was clear and the blood pressure was 140/80.

Discussion

The mode of onset of this patient's illness, the findings on liver biopsy, and negative leptospiral agglutination tests seem to permit only a diagnosis of phenylbutazone poisoning, although there were many features which suggested the possibility of leptospirosis or viral hepatitis. Severe toxic reactions due to this drug have been described in about 50% of patients. The involvement of so many different viscera in our patient suggests a hypersensitivity reaction. That such reactions occur in patients receiving phenylbutazone is made extremely probable by the microscopy findings in two fatal cases (Nathan *et al.*, 1953; O'Brien and Storey, 1954). In both patients there were multiple and widespread vascular lesions. There were also granulomatous lesions in many organs, including the pancreas. We know, however, of no other case showing transient hyperglycaemia responding to small doses of insulin.

Reports, so far, have not clarified the nature of the jaundice sometimes observed. Bourne (1953) reported three patients in whom the lesion appeared obstructive, and in another—not clinically jaundiced—granulomatous lesions were found in the portal tracts (O'Brien and Storey, 1954). In our patient the hepatitis appears to have been definitely toxic in nature.

The danger of continuing phenylbutazone after the occurrence of slight symptoms—in this case diarrhoea—must once again be emphasized.

Summary

A case of severe phenylbutazone toxicity is described. The manifestations were toxic hepatitis, myocarditis, renal lesion, glycosuria, in addition to gastro-intestinal upsets, oedema, and skin rash.

There has been complete recovery.

We are very grateful to Professor Crawford for the photomicrograph of the liver biopsy and to Dr. A. W. W. B. Woods for the electrocardiographic reports.

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Liverpool health visitors, according to the recently published report of the principal school medical officer, are unanimously of the opinion that television is playing a large part in cases where children do not receive sufficient sleep. As Professor Semple points out in his report, children who formerly were out in the streets until a late hour now have the alternative attraction of staying up late to watch television. One health visitor has found that when she advises parents to send their children earlier to bed she is frequently met with the mother's frank admission that the children are beyond her control.

FOETAL DEFECTS FOLLOWING INSULIN COMA THERAPY IN EARLY PREGNANCY

BY

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When Duraiswami (1950, 1952) described his experiments on developing chick embryos in which he produced skeletal and ocular defects by the timed injection of insulin, he added yet another possible aetiological agent in the genesis of congenital deformities to the long list which had already been compiled by Warkany (1947). He showed that a single injection within the first 48 hours after the start of incubation was likely to produce a defect in the vertebral column, whereas on the third day only the claws were liable to be affected. Furthermore, some of these induced defects were subsequently passed on to the next generation. The importance of the timing of these injections corresponds with the known fact that rubella is likely to harm the foetus only if it occurs within the first three months of pregnancy (Gregg, 1941; Swan, 1949).

In man the opportunities for similar experiments do not arise, but the widespread use of insulin as a therapeutic agent might be expected to cause similar complications. The incidence of congenital deformities in the babies born to diabetic mothers is high, but Oakley (1953), who found them in 8.6% of his series, commented that there was no evidence that hypoglycaemia was more frequent or more severe than in those pregnancies that resulted in normal infants. That insulin can hardly be incriminated here is also demonstrated by the physical anomalies and excessive foetal loss rate found in a high proportion of the pregnancies of pre-diabetic mothers (Gilbert and Dunlop, 1949).

There is one set of circumstances, however, in which excessive doses of insulin may be given for a prolonged period—namely, in the treatment of schizophrenia—and this therapy may occasionally coincide with early pregnancy, as in the following case.

Case 1

A woman suffering from schizophrenia was admitted to a mental hospital on September 28, 1949. She was given a course of deep insulin from October 12 to December 3 with 35 comas and one general convulsion, followed one month later by two E.C.T.s. Pregnancy was not diagnosed until February 3, 1950.

A child was born on April 27, weighing 6 lb. 4 oz. (2.8 kg.), four weeks before the date estimated by the consultant obstetrician. The delivery was normal, but an abnormality of the eyes was soon noticed, and tentative arrangements were made for the baby to attend an ophthalmic clinic. The grandmother cared for the baby and evidently did not seek further advice until she saw the family doctor, who referred the child, aged 3 years, to my clinic. He was blind in the left eye, had some vision in the right, was unable to feed himself, talk, or stand, and was doubly incontinent. The mother had seven normal siblings, and all four children born to them were normal, but nothing is known of the father.

On examination the child presented a picture of severe mental deficiency with wide separation of the orbits and asymmetrical development of the skull, the overall circumference of which was $20\frac{1}{2}$ in. (52 cm.). There was a divergent squint with bilateral optic atrophy, but some apprecia-