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 prediabetic 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 20½ in. (52 cm.). There was a divergent squint with bilateral optic atrophy, but some apprecia-

tion of light in the right eye. There were no signs of deformities elsewhere, and a complete radiological examination of the whole skeleton revealed abnormalities only in the skull. Dr. Kemp Harper kindly examined the films, and reported as follows: "The films show a deformed skull resulting from premature closure of the metopic part of the sagittal suture with resulting overgrowth of the parietal and occipital regions. The temporal fossae also bulge anteriorly and laterally, and there is an increase in the space between the orbits, probably resulting from overgrowth of the lesser wings of the sphenoids, and with this, or as a result of it, overgrowth of the ethmoids."

Other Case Reports

A number of mental hospitals and psychiatrists with extensive experience in this field have been asked for details of similar cases, but only two have been forthcoming in which pregnancy and insulin coma therapy were known to coincide. Dr. G. S. Nightingale supplied the following case histories.

Case 2.—This patient received insulin coma therapy and E.C.T., which apparently resulted in spontaneous miscarriage before coma level had been reached. She was probably about six weeks pregnant at the time.

Case 3.—This patient had 27 insulin comas before pregnancy was diagnosed. Therapeutic termination was carried out, a normal foetus of about 26 weeks' gestation being removed. Therapy was applied between the seventeenth and twenty-fourth weeks.

The literature has been searched, and the accompanying Table has been compiled showing the available data concerning the previously reported cases and including the three reported above.

Reported Cases of Insulin Coma in Pregnancy

Author	Treatment			Result
	Stage of Pregnancy when Started	Details	Duration	
Gralnick (1946)..	4–8 weeks	Insulin × 25 (14 comas)	6 weeks	Full-term macerated foetus
Nightingale (1953)	<8 ,,	Insulin × 1	5 days	Spontaneous abortion
Wickes (1954) ..	8 ,,	,, ×35	7 weeks	Mental defect; skull deformities
Gralnick (1946)..	10 ,,	,, ×18 (8 comas)	4 ,,	Full-term macerated foetus
McConnell (1945)	10 ,,	Insulin	—	Normal baby
,, ,,	14 ,,	,,	—	,, ,,
Nightingale (1953)	17 ,,	,, ×27	7 weeks	Therapeutic abortion; normal foetus
Goldstein *et al.* (1941)	>14 ,,	"Metrazol." Insulin	2 ,,	Normal baby

Examination of the data so far accumulated suggests that the tenth week of pregnancy is the critical stage; if treatment is given before that time foetal abnormalities are to be expected, whereas after that week the foetus appears to be no longer vulnerable.

Discussion

That insulin was responsible for the defects described in Case 1 can only be surmised. It is possible that defective germ plasm was present from the start. However, schizophrenic women do not appear to be particularly prone to produce abnormal offspring (Canavan and Clark, 1936). Hyperteleorism may be a familial disorder, but there is no evidence of genetic influence in about 60% of the cases (Brown and Kemp Harper, 1946). It is due to a defect of the sphenoid bone (Greig, 1924) occurring before ossification begins in the ninth week. In Case 1 insulin was given in the eighth week, at a time when the chondrocranium is in a vulnerable state.

Other forms of shock therapy are said not to harm the developing foetus, but there seems to be no record of E.C.T. having been given before the tenth week (Boyd and Brown, 1948). Epilepsy is also thought to be harmless in pregnancy. The above episodes are more short-lived than insulin coma therapy, and it is possible that the harmful effects of the latter are due to anoxia rather than to a specific interference with foetal tissue carbohydrate metabolism, which is the presumed mode of action in the experimental work.

Since insulin coma therapy is very rarely given in early pregnancy it is hoped that in the future the effect on the foetus will be reported in every case, so that the likelihood of the findings here reported being due merely to coincidence may be more accurately assessed.

Summary

The case is described of a mentally defective child with hyperteleorism and optic atrophy who was born to a schizophrenic woman who had received insulin coma therapy from the second month of pregnancy.

Reasons have been given for believing that insulin (or possibly the anoxia induced by it) was responsible for the foetal defects.

A study of the small number of previously reported cases suggests that insulin may be injurious only when given before the tenth week.

I am most grateful to Dr. J. S. Harris for providing me with details of the treatment of the mother in Case 1, to Dr. G. S. Nightingale for searching the files and allowing me to include Cases 2 and 3, and to a number of mental hospital superintendents and psychiatrists who have kindly searched in vain at my request for similar cases. I would also like to thank Dr. R. A. Kemp Harper for his *x*-ray report.

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THE LIVER IN ULCERATIVE COLITIS

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There have been many reports in recent years of liver damage as a complication of ulcerative colitis, and occasional references may be found in the earlier literature. The three hepatic lesions most often described are fatty change, severe inflammation in and around the portal tracts, and cirrhosis. Opinions on the frequency and significance of these changes have varied, however, and in particular the occurrence of cirrhosis has been questioned (*British Medical Journal*, 1949). We therefore decided to review all cases of ulcerative colitis which had come to necropsy in the Bernhard Baron Institute of the London Hospital from 1914 to 1953 inclusive, with especial reference to the incidence of liver lesions and the correlation of such lesions with the available clinical data.

There were 73 cases of ulcerative colitis in the years under review. Macroscopic descriptions of the liver