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
Nightingale (1953)	14 "	" × 27	7 weeks	"Therapeutic" abortion; normal foetus
Goldstein <i>et al.</i> (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 plasma 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

BY

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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

were available in all, but histological preparations were made in 39 cases only. Unless otherwise stated, therefore, the observations which follow are confined to this latter group of cases.

Pathological Findings

The incidence of the three lesions most commonly described in the literature is considered first.

Fatty Change.—The fatty livers encountered have been graded arbitrarily into mild, moderate, and severe cases. In mild lesions the fat was usually present in small foci in occasional lobules only; sometimes, however, it was more evenly distributed. In moderate cases the change was more severe and more diffuse, but less than half the parenchymal cells were affected. In severe cases at least half, usually three-quarters or more, of the liver cells were distended with large fat globules. Where a zonal distribution could be made out, the central zone was usually spared. This was not invariable, however, for in one severely affected liver the midzone was least involved, and in some mild cases the fat was confined to the central zones.

Using the above criteria, there were 25 cases in which fatty change was either absent (8) or of mild degree (17), 5 cases in which it was of moderate degree, and 9 cases in which it was severe. In one severe case, however, the patient had committed suicide by swallowing ammonia when the colonic lesion was in a healing phase, and the fatty liver was probably due to this poison.

Inflammation.—Severe diffuse inflammatory cell infiltration of the portal and periportal tissues was not present in our material. In only six cases was there a degree of cellular infiltration in excess of that so commonly seen at necropsy, and in these only a minority of portal tracts were affected—sometimes only one or two in an entire section.

Cirrhosis.—In only one of the 39 cases was a significant degree of fibrosis present. In this patient there was a carcinoma of the extrahepatic bile ducts which had caused obstructive jaundice and a suppurative cholangitis. The cirrhosis here was almost certainly of biliary type. Of the remaining 38 cases there was a slight fibrous thickening of occasional portal tracts in 4, but in none was there linking up of adjacent tracts or disruption of the lobular pattern of the liver. Cirrhosis was not found macroscopically in any of the 73 patients.

Other Lesions.—In 5 cases there were focal necroses or irregularly distributed centrilobular necroses; in one there was severe amyloidosis; in 2 there were partly organized thrombi in the left hepatic vein; and in 2 there were thrombi in branches of the portal vein. In 2 of the 73 cases examined macroscopically there was a carcinoma of the colon. Neither had hepatic secondaries.

Clinical Correlation

There were no detailed studies of liver function in the series, and clinical evidence of hepatic involvement was scanty. Moderate enlargement of the liver was recorded in four cases, in one of which there was severe fatty change at necropsy. In no case was there jaundice or splenomegaly. Of the seven cases with oedema only two had fatty livers; one of these two had a total serum protein of 3.5 g.%. In another case with oedema but without a fatty liver the serum protein was 5.9 g.%.

Since the hepatic lesion most often found at necropsy was fatty change, the clinical records were examined for factors which might cause this lesion in severe degree. After eliminating cases with coincident disease which might have damaged the liver, there remained for comparison 8 cases with severe fatty livers and 27 with moderate or minimal fatty change. Of these 35 cases 28 were in females and 7 in males, all the severely fatty livers being found in females. This difference in sex incidence is not, however, statistically significant. The onset of the disease was related to childbirth in three of the severely fatty group, diarrhoea being first noted during pregnancy in two cases and in the puer-

perium in one. All these three cases ran a rapidly progressive course, death occurring in from three to nine weeks after delivery.

The total duration of the disease was very variable and there were frequent long remissions. Of the six cases of longest duration (2 to 4½ years) only two had severely fatty livers. The terminal attack lasted from 5 to 84 weeks and there was no correlation between the length of this final episode and the degree of liver damage. It may be noted here that in six other cases in the series, excluded from this comparison because of coincident disease (2) or lack of histological preparations (4), the duration of the disease was from 7 to 29 years.

Other factors for which no significant differences could be detected between the two groups were severity of diarrhoea, loss of weight (estimated as a percentage of the standard weight for the height and age), and degree of anaemia. Anorexia was more frequently noted in the severely fatty group, as was vomiting, especially towards the termination of the illness. In no patient on whom laparotomy was performed shortly before death was there a severely fatty liver.

Discussion

Fatty change, the most common hepatic lesion found by us, was present in severe degree in 24% of the cases examined microscopically. But since it was not noted macroscopically in the remaining 34 cases, its true incidence was probably no greater than the 15% reported by Kimmelstiel *et al.* (1952) and certainly less than the 55% of Warren and Sommers (1949). Analysis of the clinical records threw little light on the pathogenesis of the lesion except that recent pregnancy was probably a contributory factor in three cases and that anorexia and vomiting may have played a part. There was no correlation between the degree of fatty change and the severity of the intestinal lesions as estimated clinically or at necropsy. It is possible that more detailed knowledge of the patients' diet would have proved fruitful.

We found no evidence to support the view of Cain and Cattani (1937) that liver failure was the main cause of death in ulcerative colitis. But while we would agree with Hardy and Brooke (1952) that the fatty livers usually produce no clinical symptoms, we regard it as probable that liver function tests would have revealed some abnormality in the more severely affected cases.

The incidence of inflammatory cell infiltration was less than we expected; for severe inflammation of the portal tracts and surrounding parenchyma has been described by several investigators, who have called it acute interstitial hepatitis (Lister, 1899), toxic hepatitis (Ross and Swarts, 1948), pericholangitis (Jones *et al.*, 1951), or interlobular hepatitis (Kimmelstiel *et al.*, 1952). In the degree found by us it would seem highly unlikely that it could interfere materially with liver function or, as has been suggested by Kimmelstiel and his colleagues, that it could eventually lead to cirrhosis. In none of our cases was there a frank portal pyaemia, a condition which has occasionally been reported as complicating ulcerative colitis (Felsen and Wolarsky, 1950; Jones *et al.*, 1951), but which is generally acknowledged to do so only rarely.

The absence of cirrhosis in our series is of interest in view of the conflicting opinions on the significance of this lesion as a complication of ulcerative colitis. A number of individual case reports have given rise to the impression that patients with ulcerative colitis are especially liable to develop cirrhosis; but in the majority of reported series (Tumen, *et al.*, 1947; Pollard and Block, 1948; Warren and Sommers, 1949; Jones *et al.*, 1951; Hoffbauer *et al.*, 1953) the incidence is only between 3.3 and 5.7%. Kimmelstiel *et al.* (1952) give a lower incidence still—namely, 1.1%. The interpretation of these figures is difficult. Tumen and his colleagues, for instance, stated that cirrhosis was present in from 1 to 6% of their routine necropsies, and yet they considered their incidence of 3.3% to be significant. Jones *et al.*, on the other hand, maintained that their figure, also 3.3%, was not in excess of that found in routine necropsies

at the Mayo Clinic. Yet Kleckner *et al.* (1952) subsequently reported cirrhosis in 18.7% of biopsy material from this same clinic.

Our series is comparable in size to those previously reported, the largest of which is composed of 93 cases. The average duration of symptoms, too, was not significantly shorter in our patients. We consider, therefore, that our figures lend strong support to the view that the incidence of cirrhosis in ulcerative colitis is not materially greater than its incidence in the population as a whole. Many of the reported cases are probably examples of post-hepatic cirrhosis, as the clinical histories and necropsy findings not infrequently suggest.

Summary

The liver lesions in 73 cases of ulcerative colitis coming to necropsy in the Bernhard Baron Institute of the London Hospital in the years 1914 to 1953 have been studied.

Severe fatty change was present in 9 of the 39 cases examined microscopically; in one of these, however, it was attributable to exogenous poisoning. Apart from recent pregnancy in three cases, and possibly anorexia and excessive vomiting in others, no clinical factors predisposing to the lesion were found.

Inflammatory cell infiltration was minimal, and, except in one case with biliary obstruction, cirrhosis was not present. It is concluded that there is little if any increased liability to the development of cirrhosis in patients with ulcerative colitis as compared with the population as a whole.

We wish to thank Professor Dorothy S. Russell and Dr. W. W. Bridgen for their helpful criticism.

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Medical Memoranda

Sensitivity to Penicillin Causing an Acute Abdominal Emergency

Reactions to penicillin occur in 1.5 to 5% of cases (Keefer and Anderson, 1950). Many are trivial, the most frequent being an urticarial rash. Other reactions described include arthralgia, lymphadenopathy, fever, and oedema (Humphreys, 1951; Wilkes, 1951). More recently fatal anaphylactoid reactions have been reported (*British Medical Journal*, 1951; Thompson, 1952; Pick and Patterson, 1953; and Mayer, 1953), and there has been an increasing correspondence about near-fatal anaphylactoid reactions.

The following case is reported, in which, after an injection of crystalline penicillin, a young woman developed severe abdominal pain and, later, urticaria, oedema, arthralgia, and lymphadenopathy.

CASE REPORT

A married woman aged 28, in the second day of the puerperium after a normal delivery, developed a small

whitlow. She was given a parenteral injection of 300,000 units of crystalline penicillin. There was no immediate reaction, but the next morning she complained of severe pain at the site of injection; the area was found to be red and swollen. It was then discovered that when she had received penicillin in 1948 her eyes and tongue had become swollen and large weals had arisen on her arms and legs.

Four hours later, 24 hours after the penicillin injection, she developed severe generalized abdominal pain, and her temperature rose to 100° F. (37.8° C.). Shortly afterwards intractable vomiting started. Tenderness and rigidity were generalized, but apparently were more marked in the right iliac fossa. A tentative diagnosis of acute appendicitis was made.

At laparotomy a normal appendix was found, but some 6 in. (15 cm.) of small bowel presented which was dark purple in colour, fading into normal-looking bowel at either side. The related omentum was swollen and haemorrhagic, and some turbid fluid was present in the peritoneal cavity. As the affected bowel appeared to be rapidly becoming necrotic, and the process seemed to be extending alarmingly, a resection was performed, including several inches of normal bowel at each side. An end-to-end anastomosis was made.

The post-operative period was stormy. Gross oedema of the periorbital tissues, face, hands, and feet developed almost immediately. Elbow, knee, wrist, and ankle joints became swollen and acutely painful. The tongue became swollen, and a generalized urticaria appeared; cervical and axillary lymph nodes became palpable, also the lymph nodes draining the site of the original penicillin injection. Under treatment with antihistamine drugs, adrenaline, and intravenous glucose-saline, the oedema slowly subsided. Four days later the joints became painless, and from that time she made a rapid recovery.

Approximately 19 cm. of small bowel, with frank purpuric haemorrhage into the mesentery and local subserous spread over the bowel, was removed. The muscularis and mucosa appeared normal. Histological examination confirmed the capillary haemorrhage into the mesentery and subserous layer of the bowel. In addition, there was acute congestion of the submucosa layer, with oedema of all layers, including the muscle.

COMMENT

Both the naked-eye and microscopical appearances of the resected portion of the bowel were those of extensive capillary haemorrhage into the mesentery and subserosa. These findings are similar to those seen in Henoch-Schönlein purpura—one of the anaphylactoid purpuras. These appearances, combined with oedema, arthralgia, and urticaria, make it certain that the purpura in this case was due to penicillin sensitivity.

Anaphylactoid purpura has already been reported in a patient receiving penicillin (Anderson, 1947). In the present case no skin purpura was seen before or after the acute abdominal episode, the reaction being confined to a small area of intestine.

In retrospect, resection would seem to have been the correct treatment in this case, despite the normal appearance of the mucosa. As in other intestinal purpuras, necrosis may well have occurred, and it appeared imminent at laparotomy.

I am grateful to Mr. L. A. Cruttenden for permission to publish this case, and to Dr. R. T. Cooke for providing an opportunity of studying the specimen of bowel.

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