LIVER DAMAGE IN ULCERATIVE COLITIS

BY

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The occurrence of liver damage as a complication of chronic ulcerative colitis has been reported occasionally during the past twenty years (Bargen and Giffin, 1930; Comfort *et al.*, 1938; Tumen *et al.*, 1947; Ross and Swarts, 1948), and it has been suggested that there is an indirect relationship between the two conditions. Tumen *et al.* reported five examples in 151 consecutive cases of ulcerative colitis and suggested that the liver damage was probably due to the chronic state of malnutrition which is associated with this disease. He also noted that whereas cirrhosis of the liver is usually found in patients of middle age and over, and most commonly in men, in the cases which he reported the age was considerably less and three of the five were women. This argument in favour of a causal relationship between the two conditions is, however, exceedingly weak, as was pointed out in an annotation in the *British Medical Journal* (1949, 1, 189). Any condition complicating ulcerative colitis, whether causally related or not, must of necessity have the same age and sex distribution as the disease itself.

It is, of course, quite possible that detectable liver damage may occur at some period of the disease and later recover. This may possibly explain the occasional but well-known finding of an enlarged spleen in ulcerative colitis when no other evidence of liver damage can be found. The significance of finger-clubbing, which is sometimes present in ulcerative colitis and in cirrhosis of the liver, is quite unknown, but its presence should certainly lead to an investigation of the liver function. It is now well established that diffuse hepatic fibrosis follows prolonged heavy infiltration of the liver cells with fat. It has been shown that this is due to a deficiency of certain lipotropic factors, principally methionine and cystine. For several reasons this deficiency may arise in cases of chronic ulcerative colitis. First, the rate of passage of the intestinal contents is increased, leading to incomplete digestion and absorption of food. Secondly, the patient's appetite in this disease is often grossly impaired and the diet therefore inadequate. Thirdly, it has sometimes been the case that inadequate diets have been prescribed in the mistaken idea that a low residue is being achieved. No such deficiency should arise provided that plenty of milk is allowed, and actually in most cases there is no reason to prohibit normal amounts of meat in the diet.

Three cases of ulcerative colitis which were associated with severe liver damage are described below. These have been seen during the past three years among approximately 20 cases. In the second case an ileostomy was performed, but it is clear that the liver was so severely damaged that the patient could not tolerate a major procedure. Whether or not an ileostomy, with the improved nutritional state which usually follows, should be performed in cases with lesser degrees of liver damage is problematical.

Case 1

A married woman aged 44 began to have diarrhoea with passage of blood in 1940; this continued without remission until 1942, when appendicostomy was performed. Diarrhoea continued, and in 1946 swelling of the abdomen started.

In April, 1947, she was admitted to hospital, where she was seen to be sallow and wasted, with slight oedema of the ankles and a grossly distended abdomen containing much free fluid.

After the ascites had been tapped a firm smooth liver edge could be felt extending two to three fingerbreadths below the right costal margin. The spleen was also hard and extended about three fingerbreadths below the left costal margin. Two barium enemas revealed the usual changes of ulcerative colitis extending proximally to the splenic flexure. There was a moderate degree of anaemia; Hb, 75%; red cells, 3,370,000 per c.mm.; white cells, 6,800 per c.mm. Plasma proteins were 7 g.%—albumin 2.6 g., globulin 4.0 g., fibrinogen 0.4 g.; alkaline phosphatase, 3 units per 100 ml.; indirect van den Bergh, 0.1 mg. bilirubin per 100 ml.

Case 2

A married woman aged 37 had a 12-years history of watery diarrhoea sometimes accompanied by the passage of blood. She became anaemic and took iron intermittently, but this seemed to aggravate the diarrhoea. In 1946 an adenoma of the thyroid was removed. In July, 1949, she was admitted to hospital complaining of great shortness of breath, swelling of the ankles, lassitude, and diarrhoea, with about ten loose or watery stools daily.

On examination she was apparently grossly anaemic, the tongue was smooth, and angular stomatitis was present. She was moderately well nourished, the fingers were clubbed, and the spleen was palpable two fingerbreadths below the left costal margin. The liver could not be felt and there was no ascites. There was slight oedema of the ankles.

Investigations.—Hb, 20%; red cells, 1,880,000 per c.mm.; white cells, 3,600 per c.mm. Stools were watery, without blood or mucus; and no pathogens were cultured. A barium enema revealed the changes of advanced ulcerative colitis in the whole of the colon. A fractional test meal disclosed histamine-fast achlorhydria. Plasma proteins amounted to 7.2 g.%—albumin 1.8 g., globulin 5.4 g.; alkaline phosphatase, 21 units per 100 ml.; thymol turbidity, 38 units per 100 ml.; indirect van den Bergh, 1 mg. bilirubin per 100 ml. Sigmoidoscopy showed the presence of much mucus and a thick granular mucous membrane with small bleeding areas to within 1 in. (2.5 cm.) of the anus.

Treatment.—Blood transfusion was given to improve the anaemia, but the general condition of the patient remained poor, and diarrhoea continued unchecked with ten to twelve watery stools daily. Ileostomy was performed on September 21, and when the abdomen was opened the presence of cirrhosis of the liver was confirmed. After operation her condition continued to deteriorate, and she developed abdominal pain and distension with a progressively deepening jaundice. Death occurred on October 3.

Post-mortem Findings

The body was that of a thin woman and showed a moderate degree of oedema of the ankles and clubbing of the fingers. The total length of the colon was reduced, and the wall was thick, rigid, and friable. There were firm adhesions between the ascending and descending colon and the posterior abdominal wall. The mucosa showed superficial ulceration extending from the caecum to the upper part of the rectum. Mostly the ulcers were small and were separated by areas of hypertrophic mucous membrane. There was a recent *Bact. coli* peritonitis, which was considered to be the cause of death.

The liver weighed 1,270 g. and had a finely granular surface with some larger nodules. The cut surface showed strands of white fibrous tissue running through the liver substance and destroying the normal architecture and surrounding irregular groups of liver tissue. The gall-bladder and bile ducts were normal. The spleen was enlarged and weighed 450 g. It was firm and rubbery and the pulp was deeply congested. The portal vein and its tributaries were normal. The lungs showed emphysema with congestion and areas of collapse in the lower lobes. The pleural cavities, heart, and pericardium were normal. The kidneys were normal apart from a few small areas of an early pyelonephritis.

Histology.—*Liver:*—There was a fine cirrhosis of the portal type. Practically all the remaining liver cells showed well-

marked fatty degeneration and there was well-marked necrosis of the liver cells in the central areas of the lobules. There was little regeneration of the liver cells, but proliferation of the bile ducts was well marked. Congestion was not pronounced and infiltration by inflammatory cells was minimal. Bile thrombi were not seen. *Colon*.—The submucosa was thickened and oedematous, and was infiltrated with lymphocytes and polymorphs. The mucosa was shed in places.

Case 3

A married woman aged 33 had a 10½-years history of diarrhoea with blood and mucus; motions numbered 14 to 20 daily in bad attacks, which were fairly well controlled by sulphonamides. She became worse in February, 1949, since when she has had fluctuating jaundice.

On examination her nutrition was fair, the conjunctivae were slightly icteric, and the fingers were clubbed. Oedema of legs and ascites were not present. Her liver was enlarged a hand's breadth below the costal margin, extending right across the epigastrium; the lower border was firm and quite regular.

Investigations.—Hb, 86%; red cells, 4,020,000 per c.mm.; white cells, 7,400; normal differential count. Urine: bilirubin +, urobilin increased. Prothrombin index, 70%; alkaline phosphatase, 13.4 units; thymol turbidity, 15 units. Plasma proteins, 8.92 g.%—albumin 3.65 g., globulin 5.27 g.%. Sig-moidoscopy showed thickening of the rectal mucous membrane with ulceration and haemorrhage. The patient subsequently improved; the jaundice has subsided, and the liver has diminished in size.

Summary

Three cases of chronic ulcerative colitis which were associated with severe liver damage are described, together with the post-mortem findings in one.

The possibility that there is a causal association between the two conditions is discussed.

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Dr. L. B. Kalinowsky, addressing the Convention of the American Psychiatric Association in Detroit, put forward the view that the likelihood of obtaining a pension initiates and perpetuates many war neuroses. If the pensions were ended, he said, the neuroses would end with them. In his address, reported in the magazine *Time*, Dr. Kalinowsky said of the defeated German armies in Russia in the winter of 1942 to 1943: "Many soldiers were unable to continue due to physical exhaustion, but hysterical symptoms were extremely rare. They did not promise any gain, and failure to stay with the group could lead only to death from exposure, or, at the best, to imprisonment by the Russians." Delayed reactions when the soldier was safe were more common but usually did not last long, again because there was nothing to gain. He pointed out that in the heaviest bombing in Britain the effects on the mental health of civilians were negligible—there was nowhere for them to escape to. In the United States Army mental misfits might be expected to have been excluded on joining, but 49% of all disability discharges from the Army were on psychiatric grounds; medical rejections on such grounds accounted for 38% of all recruits. In 1926 it was decided by German psychiatrists that pensions were a factor in prolonging neuroses from the first world war, and thereafter many of the pensioners received no further help.

Medical Memoranda

Vitamin B₁₂ (from *Streptomyces Griseus*) in Pernicious Anaemia

Vitamin B₁₂, first isolated in crystalline form from liver extracts in England by Smith and Parker (1948) and in America by Rickes *et al.* (1948a), has been shown to be effective in the treatment of macrocytic anaemias and in the prevention of subacute combined degeneration.

From the analogy that many organisms provide riboflavin for themselves, it was considered that some organisms might produce B₁₂. This was found to be the case, and the most important source so far discovered has been from various strains of streptomyces. Rickes *et al.* (1948b) obtained a crystalline material from *Streptomyces griseus*. Glaxo Laboratories have prepared concentrates from the metabolism fluid of a strain of *Str. griseus*, and it is this material that I have used on two untreated cases of pernicious anaemia. The appended results show the excellent response in each case.

CASE REPORTS

Case 1.—A married woman aged 65 complained of lassitude and a mild intermittent diarrhoea. Apart from pallor and glossitis there were no positive clinical signs. A blood count showed: red cells, 1,200,000; Hb, 29%; colour index, 1.2; reticulocytes 2.2%; white cells, 4,100, with relative lymphocytosis. Fractional test meals revealed a histamine-fast achlorhydria. The faeces contained no occult blood, and a barium enema was normal. A sternal puncture revealed a typical megaloblastic marrow. On July 1, 3 ml. of the B₁₂ concentrate was given; the response is shown below.

Date	Red Cells	Hb	Reticulocytes
June 30	1,200,000	29%	2.2%
July 1 Injection ..			4.8%
" 4			6.0%
" 5			10.0%
" 6	1,350,000	33%	17.0%
" 7	1,540,000	41%	16.0%
" 8	1,800,000	44%	15.0%
" 9	1,900,000	45%	2.8%
" 11	2,100,000	48%	1.2%
" 12	2,200,000	60%	0.5%
" 13	2,300,000		
" 14			
" 18			
" 25			

The patient had no other anti-anaemic treatment during this period.

Case 2.—A married woman aged 73 complained of generalized weakness of six months' duration. There were no positive clinical signs apart from pallor and glossitis. A blood count showed: red cells, 1,600,000; Hb 37%; G.I., 1.17; C.V., 17%; M.C.V., 106 μ^3 ; M.C.H.C. 32.4%; platelets 90,000; white cells, 3,000 (polys 34%, staff forms 2%, lymphocytes 64%); marked anisocytosis, poikilocytosis, and polychromasia. Sternal puncture revealed megaloblastic bone marrow. A fractional test meal showed histamine-fast achlorhydria. The patient was

Date	Red Cells	Hb	Reticulocytes
June 11	1,600,000	37%	2.0%
" 13		35%	2.2%
" 14			5.8%
" 15	1,300,000	37%	10.0%
" 16			15.2%
" 17	1,700,000	39%	10.7%
" 18			10.5%
" 20	2,100,000	53%	7.4%
" 21			4.6%
" 22			4.5%
" 23	2,600,000	57%	3.6%
" 25	3,100,000	67%	1.5%