

# Familial ulcerative colitis

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**EDITORIAL SYNOPSIS** A family in which eight members have or have had ulcerative colitis is presented and in them a genetic factor is considered to play a major part in the aetiology of the disease. The distribution of the disease in this family is consistent with an autosomal dominant pattern. Review of the literature suggests that a genetic influence is perhaps a more important factor in the aetiology of ulcerative colitis than previously supposed.

It is not rare for ulcerative colitis to occur in families. Jackman and Bergen (1942) record an incidence of 1.8% of familial cases in a review of 900 cases from the Mayo Clinic, and Kirsner and Spencer (1963) an incidence of 6% in a study of 1,084 cases from the University of Chicago. However, it is rare for the disease to occur in more than two members of one family. The largest familial instances on record are a family described by Houghton and Naish (1958) with four members of the family affected, and another in the series of Kirsner and Spencer also with four members affected.

The association of ulcerative colitis and regional enteritis in one family is also known. A most remarkable family is recorded by Sherlock, Bell, Steinberg, and Almy (1963) in which five members had regional enteritis and two members had ulcerative colitis.

severe attack of colitis later that same year, he was an ill man passing frequent bloody stools. Sigmoidoscopy showed changes typical of acute ulcerative colitis with pseudo-polyposis. Barium enema showed a diseased colon with pseudo-polyposis as far as the proximal transverse colon. Surgery was contemplated but a gradual remission occurred with symptomatic treatment. He did not attend follow-up clinics, but when interviewed in 1963 he claimed to have been almost free of diarrhoea since that time and refused to be examined. He still remained strictly on a low-residue diet.

III.3 B.B. had his first attack of ulcerative colitis in 1955 at the age of 38. He had several exacerbations and remissions over the next five years, eventually requiring steroids for control. In 1960, a subtotal colectomy with an ileorectal anastomosis was performed. The specimen showed typical changes of ulcerative colitis. Since that time he has put on weight, but does have a moderate degree of proctitis. More recently, he has suffered from low back pain, and radiographs suggest the presence of ankylosing spondylitis.

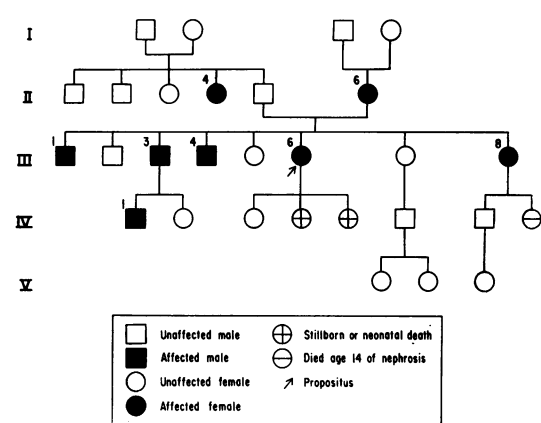
### CASE HISTORIES

III.6 B.R. is the propositus (Fig. 1).

Her first attack of colitis was in 1950 at the age of 27, and continued with exacerbations and remissions until 1955. At that time, she became pregnant, and a moderately severe exacerbation occurred. Her pregnancy was carried on in hospital but she gave premature birth to a stillborn mongoloid infant. This precipitated a most acute flare-up of her disease and she was desperately ill. An emergency ileostomy was performed, followed by a subtotal colectomy some weeks later. Eight months after this, the rectum was excised for continuing disease. Both specimens showed the changes of acute ulcerative colitis. Today she is well.

III.1 In A.B. the disease began at the age of 40 in 1955. On his first hospital admission during a subsequent

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iii.4 In G.B. the disease began suddenly in 1934 at the age of 27 in the U.S.A. where he had been living for two years. He was admitted to hospital where he was acutely ill for three months passing up to 40 bloody stools per day. He lost 80 lb. in weight during this time, and also developed generalized arthritis. Symptomatic treatment did not help, but a moderate remission occurred after three months. He left the hospital a complete invalid, and remained so for the next 18 months. During this time, he was readmitted to the hospital for a further two months with a more severe exacerbation of the colitis. He then returned to live with his family in England as he was unable to work, and over the next six months, a complete remission gradually occurred. He later returned to the U.S.A. where he has remained virtually asymptomatic since, and enjoys good health today.

iii.8 I.W. first began having attacks of bloody diarrhoea at the age of 29 in 1945. When first seen in 1952, a sigmoidoscopy and barium enema showed ulcerative colitis of the descending and sigmoid colon. She responded to treatment with a low-residue diet and bowel sedatives. Since then, she has continued to have recurrent attacks of bloody diarrhoea, which are controlled with symptomatic treatment.

ii.6 Her family states that for at least 40 years before her death, F.B. had suffered from attacks of bloody diarrhoea lasting about one month. Her last medical practitioner, who still had his notes about this patient back to 1953, when she first came under his care, records that he saw her on several occasions with moderately severe attacks of bloody diarrhoea in the presence of negative abdominal and rectal examination. He considered her to have ulcerative colitis, but she persistently refused to be referred to hospital for further investigation. She died in 1961, at the age of 82.

ii.4 The niece states that the aunt (L.A.) had died of ulcerative colitis in the Isle of Wight County Hospital in 1936, having suffered from the disease for several years. No hospital records exist but a copy of the death certificate states the cause of death at the age of 43 as 'intestinal haemorrhage due to ulcerative colitis'.

iv.1 B.B. first presented in 1963 at the age of 19 with a severe attack of ulcerative proctitis up to 15 cm. by sigmoidoscopy. Steroids were necessary to control this attack. Since then, he has had two further relapses, needing steroids for control on each occasion. He lived with his father (iii.3).

iv.2 It is interesting to note that this 18-year-old sister (V.B.) of B.B. states that her bowels move eight times a day, but she has never passed any blood. Sigmoidoscopy is normal.

DISCUSSION

Inspection of this pedigree immediately suggests that the transmission of ulcerative colitis in this family is largely controlled by a genetic factor.

If the aunt (ii.4) is excluded, the distribution of the disease in this family is consistent with an autosomal dominant pattern. In support of this pattern of inheritance are the appearance of the disease in three generations, the approximate one to one ratio (five out of eight) of affected to unaffected in the third generation, and the presence of an unaffected child of an unaffected parent of the third generation.

If the aunt is to be included, then it must be postulated that a spontaneous mutation occurred at this time. This too must have been the case in the appearance of the disease in the mother (ii.6) as both her parents lived to be 80 years of age without any evidence of disease.

A genetic transmission of the disease could be partly explained also if the gene responsible was recessive. In this case, the mother (ii.6) would have to be homozygous and therefore affected, and the father heterozygous and so unaffected. The presence of an affected or homozygous sister of the heterozygous father would be possible, presuming that both their parents were heterozygous.

The ratio of one to one in the next generation would also be compatible with this genetic pattern, known as 'pseudo-dominance'. However, the disease should not occur in the following generation as it has (iv.1) unless his father (iii.3) married yet another heterozygote for the ulcerative colitis gene. The chances of both these events occurring are very remote indeed, and so the first pattern of inheritance must be considered the more likely of the two.

The occurrence of this disease in so many members of one family by chance seems exceedingly remote. Using the same methods as Houghton and Naish (1958) to calculate the incidence of ulcerative colitis in the Southampton area, it was found to be 0.9 per 1,000. (Houghton and Naish found it to be 0.85 per 1,000 in the Bristol area.) With this incidence, the chances of even two members of a family of 10 being affected are 1 in 360,000 and of three members being affected higher than one in a million.

The question then arises as to whether some common environmental factor is present in this family predisposing it to the development of ulcerative colitis. In particular, the possibility of the disease being transmitted by a common infection, from the mother in all probability, must be considered, for Felsen and Wolarsky (1955) consider this a major aetiological factor in familial ulcerative colitis. However, although this family have lived in the same city all their lives, none were living in the same house at the time of development of the disease, with the exception of the father and son (iii.3 and iv.1). Furthermore, one brother (iii.4) developed the disease in the U.S.A. some two years after leaving England. This would seem to exclude

the possibility of the disease being transmitted by a common contact infection.

No other obvious environmental factor seems to be present. Most members of the third and fourth generation are rather anxious and introverted and are not unnaturally apprehensive about the occurrence of the disease in so many members of one family. However, this was not considered to be of significance in the aetiology.

Review of the literature reveals approximately 160 families in which ulcerative colitis occurs in more than one member. In the vast majority of instances, only two members are affected, a sibling relationship being more common than a parent-child relationship. There are only 21 instances of the disease occurring in more than two members of a family, 14 of these being recorded in the study of Kirsner and Spencer. The families with four members affected have been noted, one by Houghton and Naish where a mother and three daughters suffered from ulcerative colitis with seven other siblings unaffected, but with a nephew with regional enteritis, and one by Kirsner and Spencer where three sisters and a brother have the disease with two healthy sisters and a brother with peptic ulcer. Wigley and MacLaurin (1962) record the only instance of the disease occurring in three generations, a grandmother dying of the disease in England while a son and a grandson later developed the disease in New Zealand. Uncommonly are pedigrees recorded, and no Mendelian pattern of inheritance is evident in a study of the pedigrees available.

The not uncommon occurrence of this disease in families (and it occurs in two members of a family more often than the literature records) suggests that a genetic influence is a factor in the aetiology of this disease, but certainly not a major factor. Another well-documented fact supporting this contention is the greater incidence of the disease in the Jewish race (Paulley, 1950; Acheson, 1960; and *Ileostomy Quarterly*, 1962). It is interesting to note that ulcerative colitis has been recorded twice in twins who were very likely monozygotic (Webb, 1950;

Lyons and Postlethwait, 1948) thus representing concordance for the gene.

However, in this Southampton family, a genetic influence seems to be an important factor in the aetiology of the disease, and the distribution of the disease is most suggestive of an autosomal dominant pattern.

Follow-up of this family in later years should make the pattern of inheritance clearer. Further search for families of ulcerative colitis should be made, so that further elucidation of a genetic factor in its aetiology may be studied, for it is becoming increasingly evident that familial occurrence of this disease is much more common than previously supposed.

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