Aetiology of ulcerative colitis

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I A review of past and present hypotheses

Ever since ulcerative colitis was described by Sir Samuel Wilks in 1859, the aetiology of this intriguing condition has aroused great interest, speculation, and study. And yet, 105 years later, Broberger (1964) felt it necessary to conclude the tenth annual memorial lecture to the American Gastroenterological Association with the following words: 'Only too familiar to students of the subject; the aetiology of ulcerative colitis remains obscure.'

The very diversity of the aetiological proposals reviewed in this paper reflects the time and effort expended in seeking an answer. In a companion paper, we put forward a new hypothesis of the aetiology and pathogenesis of ulcerative colitis.

INFECTION

Even after ulcerative colitis had been separated from the infectious forms of dysentery (Wilks and Moxon, 1875), many refused to entertain the possibility of a dysenteric form of disease that was not infectious. In 1924, Bagen claimed to be able to isolate a 'diplococcus' from four-fifths of his patients suffering from ulcerative colitis. He then proceeded to inject these diplococci into experimental animals, which developed signs resembling ulcerative colitis. Bagen went on to produce a vaccine which, he claimed, was beneficial to patients suffering from ulcerative colitis.

Unfortunately, Bagen's hypothesis has not stood the test of time. His diplococoid organism was found not infrequently among control patients without ulcerative colitis. Furthermore, the organism could not be recovered from many colitis patients (Yeomans, 1921; Rolleston, 1923; Torrey, 1928). It is now believed that the 'specific' organism isolated by Bagen was probably either a pneumococcus or a streptococcus.

No sooner had the diplococcus controversy subsided, than claims were made on behalf of other organisms. Fradkin (1937) asserted that *Entamoeba histolytica* was the causal agent. Dragstedt, Dack,

and Kirsner (1941) reported that a bacterium, which rejoiced in the name of 'spherophorus necrophorus', was involved in the aetiology of ulcerative colitis. Henderson, Pinkerton, and Moore (1942) implicated a fungus, *Histoplasma capsulatum*, and, with the surge of interest in viruses, ulcerative colitis was soon added to the list of 'viral' diseases (Mones-Gallart and Sanjuan, 1935; Victor, Kirsner, and Palmer, 1950). These theories in turn collapsed in the face of a series of carefully controlled studies which showed either that the original proportion of colitis patients harbouring the suspect organism was optimistic, or that vast numbers of the non-colitic general population were also infected by the same microorganism (Meleney, 1941; Palmer, 1948; Rodanische, Kirsner, and Palmer, 1940).

In an authoritative review of these aspects of the aetiology of ulcerative colitis, Bacon (1958) concluded that neither bacteria nor parasites are the primary offenders in the disease, although they may well play an important role as secondary invaders. Bacon's argument was based on the failure of investigators to isolate any one specific organism consistently from patients with ulcerative colitis, together with the fact that antibiotic therapy has been singularly unsuccessful in bringing about a permanent cure.

MUCOLYTIC ENZYMES

Meyer *et al* (Meyer, Gellhorn, and Prudden, 1947; Meyer, Gillharn, Prudden, Lehman, and Steinberg, 1948) postulated that ulcerative colitis might result from destruction of the layer of mucus normally found on the colonic surface. Lysozyme, an enzyme found in the gastrointestinal tract of normal persons as well as of colitic patients, was claimed to be capable of destroying the mucus layer of the colon. It was shown that the lysozyme titre in the stools of colitic patients was higher than that in the stools of normal control patients, and also that the lysozyme titre in individual colitic patients varied directly in association with the clinical course of the disease.

However, these changes could very well have been the result of the disease rather than its cause, for it was subsequently shown that a rise in the lysozyme titre could be produced by diathermy of the rectal mucosa (Hiatt, Engle, Flood, and Karush, 1952). Various antilysozyme agents were used in treating patients with colitis, and while they reduced the faecal lysozyme titre most effectively, they had little effect on the clinical course of the patient's colitis (Sammons, 1951; Gray, Reifstein, Connolly, Spiro, and Young, 1950). This hypothesis fell into disrepute when it was shown that lysozyme did not materially affect human intestinal secretions (Glass, Pugh, Grace, and Wolf, 1950).

ALLERGY, HYPERSENSITIVITY, AND MILK

The production of colitis-like lesions in experimental animals by the injection of foreign antigens has recently received much attention.

Originally, interest was focused on the production of immediate hypersensitivity reactions, which are characterized by the production of circulating serum antibodies (Goldgraber and Kirsner, 1959; Kirsner, Elchlepp, Goldgraber, Ablaza, and Ford, 1959; Kirsner, 1961; Bicks and Walker, 1962). None of these workers succeeded in producing the chronic progressive lesions so characteristic of ulcerative colitis, although further studies have succeeded in producing a type of delayed hypersensitivity reaction in the colon of the experimental animal (Rosenberg and Fischer, 1964; Bicks and Rosenberg, 1964). It has yet to be shown that the experimental animal continues to produce these lesions over a number of years, a feature which is only too characteristic of patients with ulcerative colitis. Neither has it been demonstrated that the lesions produced in the experimental animal are histologically identical with those in the colitic patient. Finally the antigens which produce colitis-like lesions in the experimental animal may not do so in man (Binder, Spiro, and Thayer, 1966b).

Other evidence has been advanced in support of the allergic theory. Skyring and Roberts (1965) and Binder, Weeke, Olsen, Anthonisen, and Riis (1966c) have found that ulcerative colitis patients are more likely to develop diseases such as asthma, urticaria, and allergic rhinitis than members of the general population. Truelove and Richards (1956) and Rüs and Anthonisen (1964) have observed an excess of eosinophils in the colonic and rectal mucosa as well as in the inflammatory exudate. More recently, Binder and Hvidberg (1967) have reported an increase in the histamine content of the rectal mucosa in colitic patients. If it could be shown that

antihistamine treatment were of therapeutic value in treating ulcerative colitis, weight would be added to the allergic hypothesis. No such large-scale trial has yet been reported.

Thus the role of allergens in the pathogenesis of ulcerative colitis appears to be somewhat in the balance at the present time. We cannot leave this subject without dealing in greater detail with the most controversial of all these allergens, namely, milk.

Andresen claimed that milk contributed to the pathogenesis of ulcerative colitis in over 80% of patients, and that it was the sole cause of the disease in 40% (Andresen, 1925, 1942). Impetus has been given to these studies, largely as a result of further work by Truelove and his colleagues at Oxford. In 1961, three important items of evidence were brought forward. First it was found that some patients with ulcerative colitis experienced a remission of their colitis when milk was excluded from their diet; when milk was reintroduced they suffered a relapse. Next it was shown that antibody titre to milk proteins in the circulation was significantly raised in patients with ulcerative colitis. Finally, it was claimed that in a significantly greater proportion of colitic patients breast feeding had been abandoned in the first month of life than in healthy matched controls (Truelove, 1961; Taylor and Truelove, 1961; Acheson and Truelove, 1961).

By 1965 this group of workers had conducted a small-scale dietary trial. Patients on a milk-free diet were claimed to be better off than those on a dummy diet in that twice as many patients remained in remission throughout the year on the milk-free diet, and fewer patients suffered from relapses. The groups of patients studied were small, but elegant analytical methods supported the contention that differences in follow up were statistically significant.

A concomitant study led to the conclusion that the average antibody titre to whole milk in the group of patients with ulcerative colitis was significantly raised, although no relationship was found in the individual patient between the antibody titre to milk and the clinical course of colitis (Wright and Truelove, 1965a, b).

Thus the case in favour of milk as an aetiological factor in ulcerative colitis rests on two basic findings: (a) the circulating antibody titre to milk is significantly raised in individuals who are weaned early, and in patients suffering from ulcerative colitis; and (b) a milk-free diet is significantly beneficial to patients with ulcerative colitis.

However, the issue is not clearly resolved. In the dietary trial, the benefit derived was only just significant. Moreover, a further group of patients

on a milk-free diet plus gluten-free diet fared worse than the control group of patients.

As for the other finding, that circulating antibody titres to milk are raised in colitic patients and in early weaned individuals, this has been supported by some subsequent workers, but contradicted by other carefully controlled studies (Dudek, Spiro, and Thayer, 1965).

In Leeds we have tried to repeat the survey of Acheson and Truelove into the frequency of early weaning in colitic patients. This attempt failed because 45% of patients who were questioned did not know, and could not recall, whether they were breast- or bottle-fed. Furthermore, it is a not infrequent clandestine practice in many maternity hospitals to administer a feed of cow's milk every night to infants at around 2 am so as not to disturb the mother, and thus a 'breast-fed' baby who is delivered in a maternity hospital may have received a daily dose of cow's milk for the first two weeks of life!

Wigley and MacLaurin (1962) noted a marked difference between the incidence of ulcerative colitis in European New Zealanders and Maoris, and yet the dietary habits of the two ethnic groups are strictly comparable in so far as their milk intake is concerned. Finally, Billingham and Welchman (1966) studied two African tribes. In the first tribe, cow's milk and goat's milk are freely imbibed, and ulcerative colitis is unknown. The second tribe does not consume these milks and yet four cases of chronic idiopathic ulcerative colitis have been described in it.

Of late, the position *vis à vis* milk intolerance has become even more confused. Thus, whilst Taylor and Truelove (1961) succeeded in demonstrating circulating antibodies to milk proteins, recent workers have suggested that the beneficial effects (if any) of milk withdrawal may be due to the fact that some colitic patients develop lactose intolerance. Binder, Gryboski, Thayer, and Spiro (1966a) claim that as many as 50% of colitic patients develop intolerance of lactose.

Summarizing, it appears that milk cannot be the primary aetiological agent responsible for ulcerative colitis. However, it may well play a secondary role, producing subsequent relapses of the disease as suggested by Truelove and by Binder *et al* (1966a), but even this has yet to be fully established.

PSYCHOLOGICAL FACTORS

In 1930, a young medical student, Cecil D. Murray, published a notable paper which claimed that psychological factors might be important in the aetiology of ulcerative colitis. This hypothesis has

been summarized by Groen and Van de Valk (1956) as follows:

1 Certain individuals have a psychological make-up that renders them more vulnerable to conflicts threatening their emotional security.

2 In such patients, exacerbations of colitis are brought on by an emotional conflict in which the individual is humiliated or defeated emotionally.

3 Such persons do not respond to the emotional stimulus by action or words. The resulting emotional conflict produces the changes in the colonic mucosa, which are responsible for the clinical and pathological signs of ulcerative colitis.

Psychological and physiological evidence has been adduced in favour of this hypothesis. Many psychiatrists have observed that a large percentage of patients suffering from ulcerative colitis can be induced to confess to 'interhuman conflicts' in the immediate period before an attack of the disease (Murray, 1930; Sullivan, 1935; Palmer, 1948; Paulley, 1950, 1956; Groen and Van der Valk, 1956). Further workers, using the Rorschach and other tests, have claimed that patients with ulcerative colitis are infantile, dependent, passive, ego-centric, hesitant, and uncertain: 'One may often recognize a colitis patient in the wards by the neat way he wears his pyjamas' (Mahoney, Brockus, Ingram, Hundley, and Yaskin, 1949; Paulley, 1950; Hecht, 1952; Poser and Lee, 1963; Kollar, Caldwell, and Fullerton, 1964).

Changes in the attitude to life undoubtedly occur in patients during severe attacks of ulcerative colitis. Patients become depressed, morose, and dependent upon their clinical attendants. But who would not be depressed at the prospect of 10 or 20 bowel actions a day? Who would not become dependent upon a medical attendant whom one considered capable of alleviating these symptoms? If such depression and dependence are to be accepted criteria for a psychosomatic hypothesis, then one must carefully consider the claims of such diseases as peripheral arteriosclerosis, colonic cancer, and hiatal hernia to be psychosomatic diseases as well.

Of our own group of 465 patients with ulcerative colitis, less than 5% were attending, or had attended a psychiatrist, at any time during their life. The vast majority of the remaining patients seemed to be normal, well adjusted individuals, who showed a natural interest in their disease. As for giving a history of 'interhuman conflicts', we would not be altogether surprised if most people come into minor conflict with some other person at least once every 48 hours.

In short, we have found little evidence in our own group of patients to suggest that ulcerative colitis may be caused by emotional trauma; nor have we

formed the impression that patients with colitis differ fundamentally in their psychological makeup from members of the general population. Certainly our own findings are open to criticism on this score, because in many cases, they represent a superficial impression gained on the basis of an outpatient interview. But it is noteworthy that a recent study from the United States on colitis patients, by trained psychiatrists using sophisticated techniques, reached similar conclusions (Feldman, Cantor, Soll, and Bachrach, 1967).

Although there is little evidence to suggest that psychological factors are responsible for the initiation of ulcerative colitis, the view that emotional factors may sometimes be important in maintaining or prolonging an existing attack of ulcerative colitis receives powerful support (Drury, Florey, and Florey, 1929; Lium, 1939; White, Cobb, and Jones, 1938; Almy and Tulin, 1947; Grace, Wolf, and Wolff, 1951). The study by Grace and his colleagues demonstrated that feelings of anxiety or resentment were indeed accompanied by several changes in the colonic mucosa. The colon showed an increase in tone, a lysozyme secretion, and in intracolonic pressure; it was also observed to become hyperaemic and to secrete a thick, tenacious mucus. Furthermore, it was even claimed that in one patient with ulcerative colitis prolonged stressful discussion was able to produce mucosal erosion and ulceration.

These physiological studies thus provided support for the contention that attacks of colitis are more prolonged and severe in the presence of an adverse psychological reaction. If as Grace and his colleagues claim, the colonic mucosa of the apprehensive patient is more likely to be hyperaemic and hypermotile than that of the stoic, it is not difficult to argue from this that apprehension may be an exacerbating factor in some patients with ulcerative colitis.

This may well explain why psychiatrists from time to time obtain excellent results in treating patients with ulcerative colitis by psychotherapy alone. Most mild attacks of ulcerative colitis eventually undergo spontaneous remission without any treatment at all (Watts, de Dombal, Watkinson, and Goligher, 1966), and it seems reasonable to suggest that such attacks will remit more quickly and more readily if the patient is in a relaxed frame of mind (Paulley, 1950, 1956; Weinstock, 1962; O'Connor, Daniels, Karush, and Flood, 1964a, b; McLean, 1965).

Most physicians tacitly accept this proposition and include the process of 'reassuring the patient' as a necessary part of patient care. Whether formal psychotherapy is either necessary or desirable is

another matter, but procedures such as surgery on the frontal areas of the brain are mentioned only to be condemned.

ISCHAEMIA

It is well recognized that gangrene of the colon may occur as a complication of aortic surgery (Smith and Szilagyi, 1960; Young, Humphries, de Wolfe, and Lefevre, 1963). Recently, Marston, Pheils, Thomas, and Morson (1966) have argued that the symptoms of some patients with the so-called segmental form of ulcerative colitis may in fact be produced by less severe degrees of arterial occlusion.

Marston and his colleagues produced much interesting evidence in favour of this hypothesis. They pointed out that in some patients a vascular block could be demonstrated on selective arteriography. However, ischaemic changes may occur in the colon even in the absence of a demonstrable localized vascular block (Engelhart and Jacobson, 1956; Cooling and Protheroe, 1958; Marston, 1962). Changes identical to those described by Marston and his colleagues have been produced experimentally in dogs, and by arterial occlusion in man (Boley, Schwartz, Lash, and Sternhill, 1963; Engelhart and Jacobson, 1956). Significantly, the most severe changes in Marston's patients were found at a point in the colon where the vascular supply was most precarious (Griffiths, 1956). Finally, and most impressively of all, it was claimed that cases documented in the literature as idiopathic segmental colitis (Kellock, 1957) showed clinical and pathological features identical to the features of the patients described by Marston.

Some cases of segmental colitis, where the lesions are most severe at the splenic flexure, and where there is no suggestion of Crohn's disease of the colon, may therefore be due to vascular changes. However, such cases form an extremely small percentage of the total group of patients with idiopathic ulcerative colitis. It will also be appreciated that the aetiological problem has merely been referred; the new question is raised, what is the cause of the vascular changes?

AUTOIMMUNITY

One controversy or another about autoimmunity has raged ever since 1904 when Donath and Landsteiner declared a paroxysmal cold haemoglobinuria to be due to autoimmune phenomena. It was therefore only a matter of time before autoimmunity was declared to be responsible for ulcerative colitis, and indeed, certain facts strongly favour such a

possibility. The pathological changes in the colitic colon are compatible with an autoimmune phenomenon (Kirsner, 1958), and colitis frequently accompanies other diseases which are believed to be autoimmune, such as haemolytic anaemia (Lorber, Schwartz, and Wasserman, 1955). In addition, ulcerative colitis can be controlled by drugs such as steroids and ACTH which are effective in the treatment of autoimmune disease (Truelove and Witts, 1954, 1955, 1959).

One of the principal difficulties in this field is the lack of general agreement concerning the pathogenesis of autoimmune diseases. There are two main contending theories. In the first, it is postulated that changes in the antigenic status of the target tissue elicit the production of autoantibodies: this is disturbed-antigen autoimmunity. In the second, the changes that initiate the disease are said to occur in mesenchymal stem cells to produce the growth of a forbidden clone (Burnet, 1959, 1965) of autoantibody-producing cells: this is disturbed-tolerance autoimmunity. Each may be applicable in the appropriate circumstances.

In 1957, Witebsky and his colleagues (Witebsky, Rose, Terplan, Paine, and Egan, 1957) proposed certain criteria which should be met before attributing the pathogenesis of any particular disease to an autoantibody. These criteria have been set out as follows:

- 1 The direct demonstration of free circulating autoantibodies (or of cell-bound autoantibodies by indirect means) that are active at body temperature.
- 2 Recognition of a specific antigen against which this antibody is directed.
- 3 The production of antibody against this same antigen in the experimental animal.
- 4 The demonstration of pathological changes in the corresponding tissues of actively sensitized experimental animals, which are basically similar to those in the human disease.

It will be noticed that these criteria are silent with respect to the all-important issue of cause and effect, although 3 and 4 appear to be predicated on the disturbed-antigen view of autoimmunity.

The first autoimmune studies in the field of ulcerative colitis are widely attributed to Broberger and Perlmann (1959). Using an extract of foetal colon in tissue culture, they were able to show haemagglutinating antibodies to the colonic mucosa in the sera of no fewer than 20 out of 30 children with ulcerative colitis. Less frequently, such antibodies to colonic mucosa were found in adults, and in control sera taken from other non-colitic children presumed to be suffering from autoimmune diseases such as Hashimoto's disease of the thyroid.

Unfortunately, when various other workers attempted to repeat this experimental work, the findings differed considerably, possibly because of variations in technique (Edgar, 1961; Gray, Walker, and Thompson, 1961; Bernier, Lambing, Terris, and Cornelis, 1962; Henriksen, Gunderson, and Opsahl, 1962; Bregman and Kirsner, 1966). However, recent studies in our own department have confirmed Broberger and Perlmann's findings *in vivo*, and they indicate that immune gamma globulin is fixed in the colon in the living colitis patients (de Dombal, 1967).

Broberger and Perlmann then showed that antibodies could be isolated from colonic lymph nodes which reacted with extracts of colonic tissue (Perlmann and Broberger, 1960). Next, they were able to show that antibodies were present in the sera of some patients with ulcerative colitis which reacted with an antigen in the cytoplasm of colonic epithelial cells: these findings were confirmed by Klavins (1963) and by Koffler, Minkowitz, Rothman, and Garlock (1962).

Finally, Perlmann and Broberger showed in 1963 that leucocytes from patients with ulcerative colitis had a cytotoxic effect upon foetal colon cells in tissue culture, an effect which was inhibited by pretreatment of the lymphocytes with colon antigen. This finding too has been recently confirmed by Watson, Quigley, and Bolt (1966) and *in vivo* by Fink, Donnelly and Jablowski (1967).

Thus the first and second of Witebsky's criteria appear to have been fulfilled by these studies, although it should be noted that in recent studies little correlation was observed between the clinical course of ulcerative colitis and the incidence of circulating antibodies to colon (Harrison, 1965; Wright and Truelove, 1966).

The remaining two of Witebsky's criteria are as yet unfulfilled, but their relevance is, perhaps, dubious. Furthermore, the relation of the circulating autoantibodies to the causal mechanism remains unanswered. In 1961, LeVeen and his colleagues managed to produce a type of ulcerative colitis in dogs by injecting an anticolon antiserum prepared from either the duck or the rabbit. However, as Kraft, Bregman, and Kirsner (1962) point out, the histological changes observed in the colitic patient, and the use by LeVeen and his colleagues of Freund's adjuvant for the development of adequate titres of rabbit antidog colon serum, renders the task of evaluating their evidence somewhat difficult.

Lately, it seemed that the aetiological wheel might have come full circle. Broberger (1964) and Perlmann, Lagercranz, and Gustafson (1965) showed that *E. coli* 0 14 and extracts of colonic mucosa had a similar antigenicity, and they suggested that stimulation of

the immune system of the body by *E. coli* 0 14 might lead to the development of antibodies which reacted not only with the bacterium, but with the colonic mucosa as well to give rise to the lesions of ulcerative colitis. This proposal has since been challenged by Stefani and Fink (1966, 1967), who have been unable to confirm the antigenic similarity between colonic mucosa and *E. coli* 0 14 postulated by previous workers.

In conclusion, it seems clear that some patients with ulcerative colitis develop circulating antibodies to cytoplasmic constituents of colonic mucosal cells. However, the evidence cited so far does not even begin to bear on the crucial aetiological problem. Are the autoantibodies to the colonic mucosa the cause, or the result, of the pathological changes in the bowel? We shall try to answer this key question in our next paper, where we shall also discuss the role of genetic factors, and the contribution of mast cells.

SUMMARY

A critical review is given of hypotheses which have been advanced to explain the aetiology of ulcerative colitis.

Bacteria, parasites, fungi, viruses, and destructive enzymes have all been suggested as causes of ulcerative colitis. Today there is little support for the view that any of these agents is a necessary and sufficient cause of the disease.

Allergy, notably to certain foodstuffs such as milk, has been investigated as a cause of ulcerative colitis. Some patients benefit from the withdrawal of milk from their diet, but many others do not. Statistically, the benefits of milk withdrawal are only marginally significant.

Although relapses of ulcerative colitis can undoubtedly be aggravated by psychological factors, there is no evidence that psychological stress *per se* can initiate the disease process.

Recently, it has been repeatedly asserted that ulcerative colitis is an autoimmune disease. Experimental evidence in favour of this possibility is critically analysed.

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II A new hypothesis

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None of the hypotheses reviewed in our previous paper tackled the pathogenetic issues posed by the sex and age distributions of ulcerative colitis. In this paper we show that the age patterns of seven large clinical series, from three different continents, display some remarkably consistent features. From a detailed analysis of the epidemiological statistics, and from clinical, genetic, and serological evidence, we are able to put forward a new aetiological theory.

We shall argue that ulcerative colitis develops only in those people who have a genetic predisposition to the disease. Evans and Acheson (1965) have previously distinguished between early- and late-onset cases, and our studies, both of the age distributions, and of the clinical course of the disease in early- and late-onset patients, confirm the idea that at least two distinctive groups are predisposed.

Given the diathesis, the initiation of ulcerative colitis appears to depend on random intrinsic events, of which the average rate of occurrence is effectively invariant at different times and in widely separated environments. Following Burnet (1959, 1965), we suggest these intrinsic random events correspond to somatic gene mutations in mesenchymal stem cells. Ulcerative colitis appears to belong to the general class of disease widely known as 'disturbed-tolerance autoimmunity'. However, many reasons can be adduced for rejecting the notion that immunoglobulin autoantibodies constitute the primary causal agents in idiopathic 'autoimmunity' (Fahey and Goodman, 1964; Samloff and Barnett, 1965; Bernier and Hines, 1967; Burch, Rowell, and Burwell, 1968). From our serological findings (de Dombal, 1967a, b), we conclude that if the primary 'autoantibodies' are humoral, they are more likely to be found in the α_2 -globulin, than in the β - or γ -globulin electrophoretic fractions. Accordingly, we suggest that 'autoaggressive' is, perhaps, a less misleading description than 'autoimmune', for it conveys no prejudicial overtones regarding the identity of the cell system(s) producing the primary pathogenic agents.

SEX-SPECIFIC AND AGE-SPECIFIC ONSET RATES

Aetiological theories have been tested for their ability to account for the sex and age distributions of diseases that are widely believed to be 'auto-immune', such as chronic discoid and systemic lupus erythematosus, inflammatory polyarthritis, and myasthenia gravis (Burch, 1966b, 1968; Burch and Rowell, 1965a, 1968). Only Burnet's 'forbidden-clone' theory of disturbed-tolerance autoimmunity (Burnet, 1959, 1965; Burnet and Holmes, 1965) provides a convincing interpretation of the age patterns of such diseases.

Briefly, this theory states: (1) predisposition to 'autoimmune' disease is genetically determined; (2) the growth of forbidden clones is initiated by the random occurrence of specific somatic mutations in mesenchymal stem cells; (3) forbidden clones synthesize humoral or cellular 'autoantibodies' that attack tissues bearing complementary antigens; and (4) a latent period necessarily intervenes between the last initiating somatic mutation and the first manifestation of the disease.

We find the duration of the latent period often depends, to some extent, on environmental factors (Burch, 1966b). Granted certain provisos, the age patterns of all spontaneous disturbed-tolerance autoimmune diseases—or better, autoaggressive diseases—are expected to conform to certain simple mathematical rules (Burch, 1966a, b). For example, we should be able to describe age-specific initiation rates by stochastic equations such as 1 and 2 below.

Ideally, statistics for age analysis would comprise every confirmed case, by sex and age at first onset, in several very large, geographically separated, and precisely defined populations, at different secular times. Needless to say, such ideal data do not exist, but provided there is no systematic age or sex bias in the admission of patients to a clinical series, then no distortion of the age pattern will arise from selection factors. Indeed, clinical series and population studies lead to the same general conclusions (Burch, 1968).

We have analysed data from seven clinical series