

Prediction of acute relapse of Crohn's disease: A study of host nonspecific immune reactivity

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E RENÉ. Prediction of acute relapse of Crohn's disease: A study of host nonspecific immune reactivity. *Can J Gastroenterol* 1993;7(2):226-231. In Crohn's disease, there is evidence of activation of immunological effector mechanisms in the mucosa. Currently, it is not clear if the activated immunological processes are an appropriate response to an as yet unidentified pathogen or a pathologically increased response to a relatively otherwise innocent challenge. The tissue damage characteristic of Crohn's disease results from T cell-mediated granuloma formation, suggesting a delayed-type hypersensitivity reaction. However, data regarding cellular immunity in Crohn's disease are not conclusive. Depression of delayed hypersensitivity was found by several authors, while others have reported normal skin reactivity. It is still largely unknown whether hypo-responsiveness, if present in Crohn's disease, is related to clinical activity of the disease or caused by nonspecific mechanisms such as malnutrition. A kinetic approach to the host factors was designed which analyzed the change of skin delayed hypersensitivity reaction associated with three main evolutive events of Crohn's disease: period of stable remission; period preceding acute flare up; period preceding and following surgical resection of the diseased gut. Fluctuations between anergic and hyperergic states were observed during Crohn's disease evolution. The influence of the host's immune response quality (expressed by skin delayed hypersensitivity) on the clinical course of Crohn's disease is discussed, and the following hypothesis proposed. The course of Crohn's disease would be dependent on the balance of phases of 'hyperergy' during which the pathogenic agents (not necessarily specific) would easily induce acute flare-up with a high frequency of relapses, and alternatively phases of 'hypo-ergy' during which the pathogenic agents would hardly induce acute flare-up resulting in a low frequency of relapse. Alternatively, this hypothesis, based on differences in the host response, may be the explanation of individual variation in the course of Crohn's disease. The ability to mount an immune reaction would be an individual characteristic and would lead to the classic dual pattern of the course of the disease consistently found in different groups of patients, namely continuous course as opposed to intermittent or inactive disease.

Key Words: Crohn's disease, Chaos theory, Recurrence activity, Pathophysiology

Prédiction des récidives au cours la maladie de Crohn : Étude de la réactivité non spécifique de l'hôte

RÉSUMÉ: Une activation du système immunitaire digestif a été montrée au cours de la maladie de Crohn (MC). Actuellement, nous ignorons s'il s'agit d'une réponse appropriée à un pathogène non identifié ou d'une réponse accrue à une

RELAPSES OF CROHN'S DISEASE APPEAR to be almost random. Although a reproducible measure of a patient's disease activity appears to be possible (1-4), so far, no indices (clinical or laboratory based) have been consistently shown to predict the likelihood of a patient in partial or complete remission suffering an acute exacerbation. The concept of a link between the host nonspecific immune reactivity and the course of Crohn's disease is discussed here, defining first a validity domain and second its role in the clinical expression of Crohn's disease.

DEFINITION AND VALIDITY DOMAIN OF A LOGICAL STRUCTURATE RELATING CLINICAL AND BIOLOGICAL CHANGE DURING CROHN'S DISEASE EVOLUTION

During the past 10 years new data on gut immunology and inflammatory mediators have led to a newly acquired body of information. Unfortunately, it seems to the clinician, forced to deal with the reality of the clinical aspects of Crohn's disease, that the current new basic information leads to an increased difficulty in structuring the knowledge concerning the relationship between the basic immunological data and the clinical pattern of Crohn's disease. Paradoxically, this increases the feeling that clinical relapses of Crohn's disease appear to be almost random.

To analyze further the validity domain of establishing a logical relationship between biological and clinical observations it is necessary to

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stimulation habituellement banale. L'étude cinétique des réponses immunitaires de type hypersensibilité cutanée au cours des périodes de rémission stable, des périodes précédant les poussées, des périodes précédant et suivant la résection chirurgicale de l'intestin atteint montre des fluctuations entre anergie et hyper-énergie. L'hypothèse suivante peut être proposée : l'évolution de la MC dépendrait de l'alternance de phases d'hypersensibilité pendant lesquelles les agents pathogènes (pas nécessairement spécifiques) induiraient des poussées avec une fréquence élevée et des phases d'hyposensibilité pendant lesquelles les agents pathogènes n'indueraient pas ou peu de poussées. Les différentes capacités à développer une réaction immunitaire pourraient constituer une caractéristique individuelle qui aboutirait aux deux formes évolutives décrites au cours de la MC : une forme d'évolutivité rapide et une forme d'évolutivité lente.

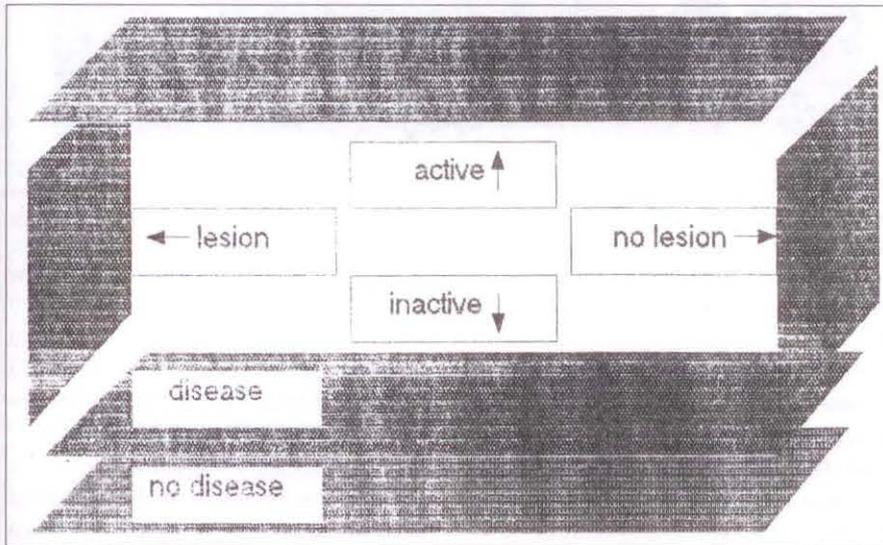


Figure 1) Schematic representation of Crohn's disease evolutive events differentiating acute flare-up from quiescence, presence and absence of lesion, and disease from no disease

establish a logical structure using a clinicobiological scheme. A relevant scheme would have to detect or measure parameters that reflect three features (Figure 1): first, an enhanced susceptibility to Crohn's disease compared with normal subjects; second, the development of a lesion compared with the absence of a lesion; third, the development of an acute flare-up compared with remission or quiescence. This scheme could be then applied to an iterative assessment of the evolution of Crohn's disease.

Comparison of measured parameters (serological or mucosal, and increased, unchanged or lowered) would then lead to a chart suitable for comparing the presence or absence of evolution, as well as the presence or absence of lesions and control subjects to patients with Crohn's disease. When collecting the different data to construct the

chart, it will be realized that all data on immunology and inflammatory mediators possess a common pattern; each factor concerns isolated markers belonging to a complex which is just a small part of a new complex, again representing only part of the disease.

Currently the construction of such a chart would be jeopardized by the number of unknown intermediary mechanisms which preclude the establishment of a logical link between those mechanisms.

Hence the question – would the recognition of all the parameters of a specific marker of Crohn's disease pathogeny help in predicting acute relapses of Crohn's disease? Systemic lupus erythematosus can be used as an example since the majority of patients in remission have normal immunological tests (5). An increase in anti-DNA titres is followed in half of the cases by

the reappearance of disease activity within an interval ranging from several weeks to several months. When increased anti-DNA antibody titre is associated with a decrease in complement level, the clinical relapse occurs earlier (one to three months) (6). The study of the correlation between the occurrence of clinical relapse and the reappearance of immunological abnormalities showed that only 10% of patients with complete clinical long-lasting remission still had antinuclear factors and/or hypocomplementemia. In conclusion, these studies indicate parallels exist between DNA binding activity and the clinical course in some patients. "Enormous exceptions are observed though, and those exceptions preclude the use of this test as a therapeutic guideline in systemic lupus erythematosus" (6).

So far this type of statement only fuels the disappointed clinician's scepticism about the actual relevance of basic science to the practical management of patients. Nevertheless, leaving the medical field, this kind of problem, dealing with the pitfalls of prediction, has already been met and very interestingly theorized in the field of physical knowledge, particularly as applied to meteorological forecasting. Failures in such systems led initially to questions regarding the validity of the classical determinism theory of Laplace. Recently, another theory – the theory of chaos (7) – has been used to explain the pitfalls of the theory of Laplace. Both the theory of Laplace and the theory of chaos can be explained through a simple analogy: a billiard table or pool table with a ball and four bumpers (Figure 2). According to Laplace; at any given point if one knows the totality of the present force and the law of the changes when meeting a bumper, then one will get to know the past and the future. Astronomy, for example, represents a system which fits well with this kind of prediction. The same device can be used to explain the theory of chaos. By making a new hit (black line compared with white line in Figure 2) sufficient to introduce a very slight change in the initial trajectory, eventually the white trajectory hits a

bumper whereas the black does not. From now on, the new trajectories have nothing to do with each other. This is a simple example of the emergence of chaos. In experimental science, uncertainties in observation lead to slight changes in biological prediction whose cumulative effect may determine chaotic phenomena. As a consequence of the chaos analysis, the search for a biological link between observed phenomena should select biological events which stand within short intervals. This avoids the emergence of chaotic phenomena due to cumulative observation uncertainties. Since currently the definition of acute relapse in Crohn's disease is mainly clinically based, biological events preceding relapses should be close to the relapse phenomena and be sensitive enough to exhibit easily observable changes before an attack.

In order to delineate what short intervals in Crohn's disease pathogeny could be, a simple chart has to be established linking the input factors and the output factors (Figure 3). This chart includes a hypothetical intermediate step which includes three sections remaining to be discovered in Crohn's disease. The first involves genetic factors that will not be discussed further. The second involves the lymphoid tissue localized not only in the gut but also in other tissues, such as skin, bronchoalveolar tissue, joints, buccal mucosa and associated lymphoid tissue, that can be designed as 'barrier associated lymphoid tissue', since it stands on a barrier between self and nonself. The 'barrier associated lymphoid tissues' can be compared to 'non-barrier associated lymphoid tissues', which are found in the various parenchyma – liver, heart, brain, kidney, muscle, bone – all situated deeply in the organism and not on the 'barrier' area. The third feature is the interaction of B and T cells in determining the immune reaction. To avoid approaching them separately and directly, it is necessary to test them in a 'steady-state'. This steady-state is simply the result of an equilibrium between an increase in the reaction intensity by stimulating factors (whatever they are) and a decrease

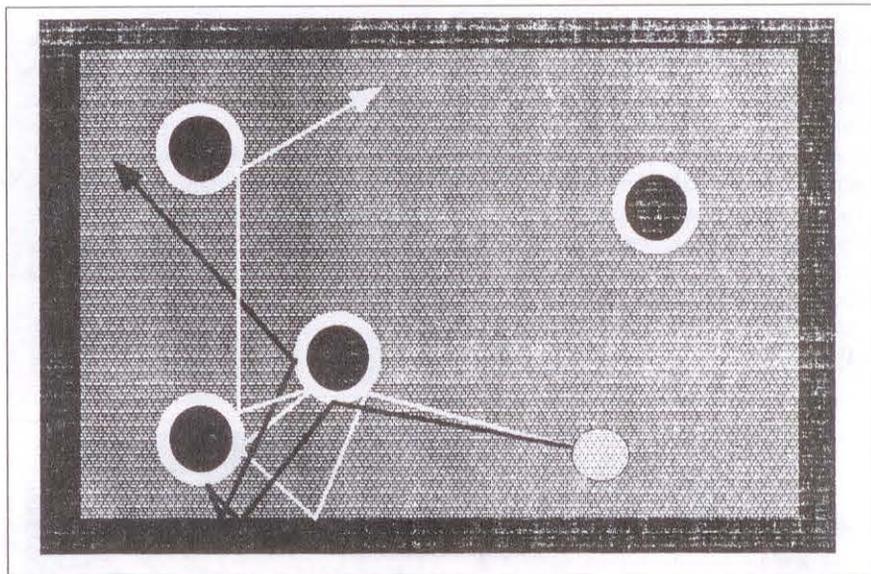


Figure 2) Schematic representation of the chaos theory applied to the pool table system with a ball and four round stop pieces. The two trajectories (black and white) slightly differ initially, the discrepancy increases with the trajectory development, up to a certain point where the white trajectory hits a round stop piece whereas the black does not. After this point the two trajectories have nothing to do with each other

in the reaction intensity due to inhibitory factors such as negative feedback. It can be postulated that if a test assessing the level of this steady-state can be formed then, it should be possible to predict Crohn's disease activity. To test the relevance of this postulate, another pathological model, the modifications of skin delayed hypersensitivity during leprosy (8), will be studied.

The immunoregulation of the chronic granulomatous reaction during leprosy as studied by skin delayed hypersensitivity is summarized in Figure 4, this shows a steady-state level of the granulomatous reaction resulting in granulomatous tissue formation and destruction. At the bottom are the anergic, lepromatous and multibacillary forms. At the top, the hyperergic, tuberculoidosis and paucibacillary forms. Fluctuations between the anergic and the hyperergic states are well known during leprosy evolution. Therefore, the question arises whether such fluctuations could be observed during Crohn's disease evolution, and whether the host's immune response (expressed by skin delayed hypersensitivity) could influence the course of Crohn's disease.

HOST FACTORS AND THE CLINICAL EXPRESSION OF CROHN'S DISEASE

The host response has been studied extensively in leprosy (since *Mycobacterium leprae* is remarkably nontoxic and weakly virulent [8]), and the host factors (as expressed by skin delayed hypersensitivity) have been shown to play a role in the clinical expression of leprosy (9). A continuous decrease in immune reactivity from the tuberculoid towards the lepromatous end of the scale was found (4). This suggests that the clinical manifestation of leprosy is determined by the capacity of each subject to mount a cell-mediated immune response to *M leprae* (8). In Crohn's disease, data regarding cellular immunity are not conclusive (depression of delayed hypersensitivity was found by several authors [10-13] others reported normal skin reactivity [14-18]). In vitro hyporesponsiveness in the lymphocyte transformation test has been documented (19-22) but many reports of unimpaired in vitro lymphocyte reactivity have also been published (17,22,23-25). To what extent the discrepancies mentioned are due to differences in technique is unsolved. Furthermore it is still largely unknown

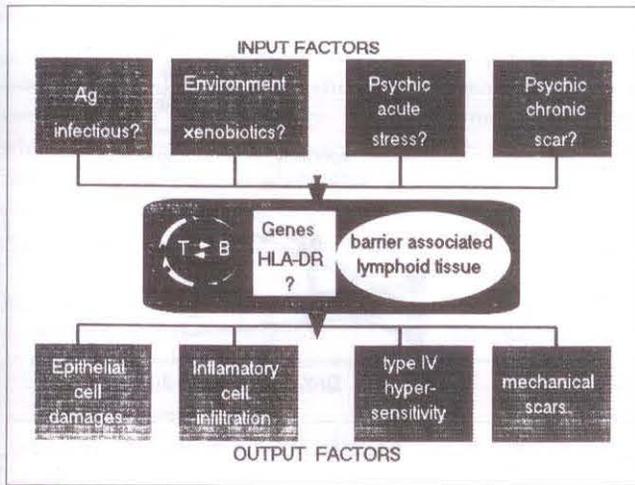


Figure 3) Schematic representation of Crohn's disease physiopathology, the aim of which is to group the different phases, to structure a close enough relationship to avoid the emergence of chaotic phenomena, when deducting links in between

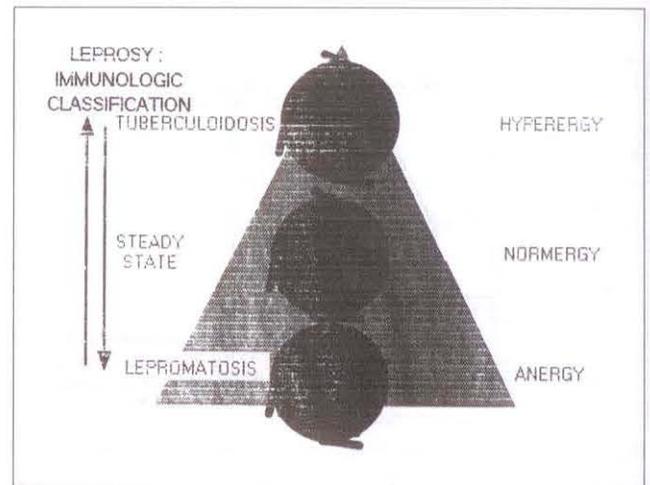


Figure 4) Schematic representation of the immunological classification of leprosy as studied by skin delayed hypersensitivity: anergic, lepromatosis and multibacillaries forms at the bottom and, at the top, the hyperergic, tuberculoidosis and paucibacillaries forms of the disease

whether hyporesponsiveness in vitro or in vivo, if present in Crohn's disease, is in any way related to clinical activity of the disease, or caused by nonspecific mechanisms such as malnutrition (26).

To bring new insights to the T cell mediated response during Crohn's disease, a kinetic approach was designed for the host factors analyzing the change in skin delayed hypersensitivity associated with three events of Crohn's disease: the period of stable remission; the period preceding an acute flare-up; and the period preceding and following surgical resection of the diseased gut. For this, the evolution of skin delayed hypersensitivity was studied prospectively every three months over a one year period (using the seven-antigen multiple-puncture test [Merieux Institute, Lyon, France]). During this period six patients remained in remission, three patients had a recurrence and two patients were followed through the pre- and postoperative course of Crohn's disease treated by curative resection. For controls, eight normal subjects without gastrointestinal complaints and four otherwise normal subjects undergoing appendectomy for acute appendicitis were studied in a similar fashion. Crohn's disease was diagnosed on the basis of a previously validated score (27). Activity was measured by the Crohn's disease activity index (CDAI) in its second ver-

sion (28). An acute flare-up was defined by a CDAI of 200 or greater combined with a change of at least 100 CDAI points. Since malnutrition may be associated with reduced immunological competence in patients with Crohn's disease (26), the standard anthropometric measurements, including height, weight, mid-arm circumference and skinfold thickness were systematically assessed during follow-up. Mid-arm circumference was measured at the midpoint between the acromioclavicular joint and olecranon process. Skinfold thickness was measured by Holtain callipers at triceps, biceps, subscapular and suprailiac regions (29). Body mass index was calculated as kg/m^2 . Finally, since immunosuppressive therapy reduces immunological competence during Crohn's disease (21-24) medical therapy was withdrawn 15 days before the study entry. When patients experienced an acute flare up during the follow-up they were started on oral prednisone metasulphabenzate and the skin test survey was interrupted until the end of steroid treatment. Three patients developed an acute flare-up during the first year of the survey (respectively three, six and six months after entry in the study). All three were or became negative within the three months before the occurrence of the acute flare-up. However, this pattern was not

specific, since two of the six patients with stable remission exhibited the same evolution and did not develop relapses. None of the eight control subjects exhibited the same immunological pattern. In conclusion, the non-reactive skin tests seemed specific to Crohn's disease evolution compared with normal subjects. Changes were sensitive enough to predict an acute flare-up in the next three months, although they were not specific.

To study the influence of the nutritional changes of the skin tests modification, the data concerning stable remission and the period preceding acute flare-up was expressed as a function of the body mass index (Figure 5). The skin test results are expressed as a percentage of the total of the nutritional class (stratified in four classes of body mass index). In control subjects (Figure 5, right) a 100% positive tuberculin skin test and 0% negative was observed; this result is common for all four classes which are above the normal nutritional value. Similarly (Figure 5, left), in the class above the normal nutritional value, in the Crohn's disease group 100% positive tests and 0% negative were observed. When the body mass index decreases below normal value, a regular increase in the negative tests is observed. This is in good agreement with the recent data from the St. Thomas' Hospital group in

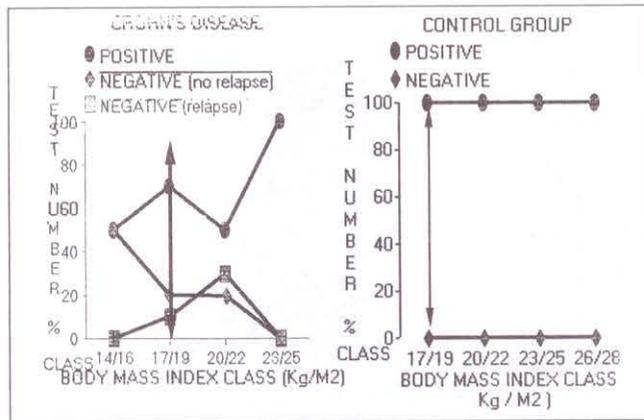


Figure 5) Relationship between nutritional changes and tuberculin skin tests in the nine patients with Crohn's disease (left panel) and the eight controls (right panel). Positive and negative test number are expressed as percentage of the total of tests performed in the subjects of the same class (stratifying the body mass index); vertical double arrow is the normal body mass index value

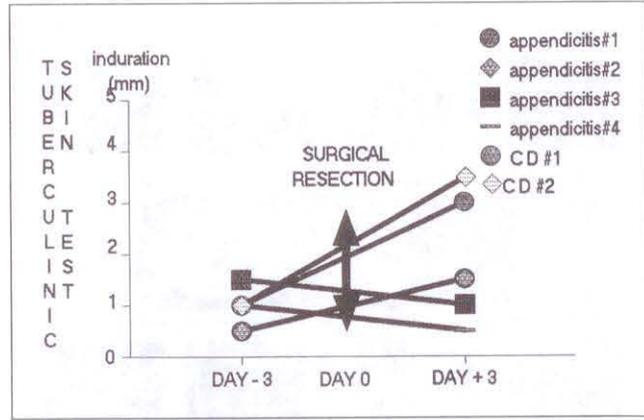


Figure 6) Skin delayed hypersensitivity (in response to tuberculin) modification after surgical resection of the diseased gut in two stenotic Crohn's disease patients and four otherwise normal subjects going through appendectomy for acute appendicitis

London, United Kingdom (26). When the negative tests in patients who will not relapse are differentiated from the negative tests in patients who will relapse, in the class above normal nutritional values, most of the 'negative patients who will relapse' are found. This is in contrast to the classes below normal nutritional value where most of the 'negative patients who will not relapse' are found. This might mean that the skin test negativity in normal weight patients is not due to malnutrition but to immunological changes preceding acute flare-up.

The findings of this pilot study need to be confirmed in a trial involving more patients. However, if this observation is confirmed, the decrease of skin delayed hypersensitivity just before the occurrence of flare-up without nutritional modification would favour the hypothesis of spontaneous fluctuation of immunological reactivity during Crohn's disease. Another argument for the existence of fluctuation of delayed hypersensitivity during Crohn's disease is brought by the post surgical observation. In fact, the two patients who underwent curative surgical resection for symptomatic segmental ileal stenosis exhibited a unique change of skin delayed hypersensitivity, with a rapid shift from negative toward positive skin test (Figure 6). On the contrary, none of the four surgical control subjects who underwent appen-

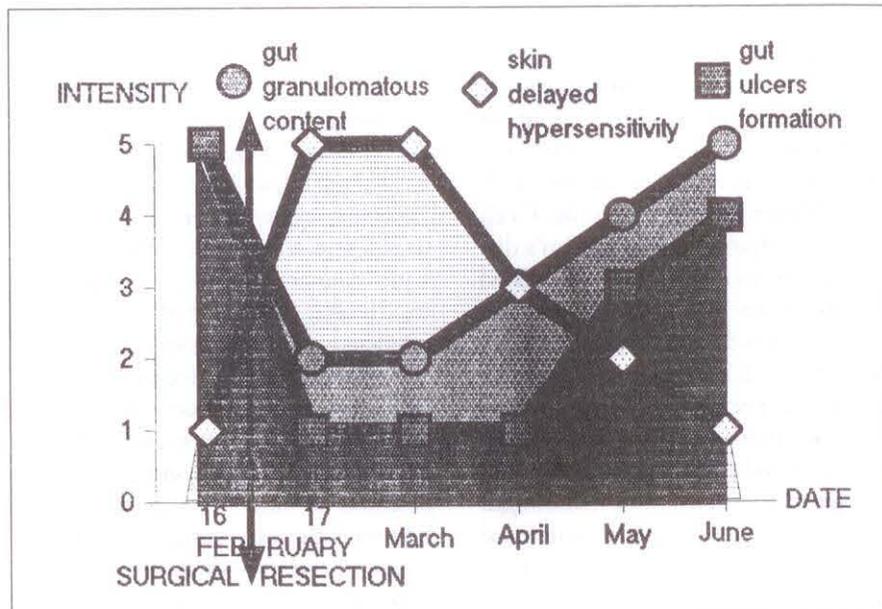


Figure 7) Hypothetical diagram of the pre- and post-surgical events during Crohn's disease. Gut resection would induce a quick (within days light grey area) reappearance of the skin delayed hypersensitivity, and a secondary (probably within weeks dark grey area) reappearance of endoscopic lesions as far as the digestive flux is present. The post-resection resaturation of gut hypersensitivity (pale grey area) would then lead to a negativation (not due to nutritional deficiency) of skin delayed hypersensitivity by a hypothetical negative feedback mechanism

dectomy showed a change in their negative skin test. This fits well with the suppression of a negative feedback combined with the gut resection.

Taken together, these facts can be interpreted on a synthetic and schematic diagram (Figure 7) where surgical resection of Crohn's lesions is associated with a quick (within days, light area in Figure 7) reappearance of skin delayed hypersensitivity. This is in con-

trast with the secondary (probably within weeks, dark area in Figure 7) reappearance of endoscopic lesions as far as the digestive flux is present. The post surgical events are presumably due both to luminal antigen reintroduction with flux and, as suggested here, to the restoration of gut hypersensitivity (pale area in Figure 7). This, in turn, would lead to a negative skin test (independent of nutritional changes). Ac-

cordingly the following hypothesis is presented. The course of Crohn's disease would be dependent on the alternating phases of hyperergy during which the pathogenic agents (not necessarily specific) would easily induce an acute flare-up with a high frequency of relapses and alternating

phases of hypo-ergy, during which the pathogenic agents would hardly induce acute flare-up resulting in a low frequency of relapses. Finally, the same hypothesis based on differences in the host response may also explain the individual variations in the course of Crohn's disease course. Differing

abilities to mount an immune reaction would be an individual characteristic and would lead to the classical dual pattern of the course of the disease consistently found in different groups of patients with Crohn's disease, namely continuous course as opposed to intermittent or inactive.

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