AUTO-IMMUNE DISEASE

II. PATHOLOGY OF THE IMMUNE RESPONSE*

BY

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In the first lecture I gave an outline of a theoretical approach to immunology which I claimed had special virtues for the understanding of some immunopathological states. Its basic contentions were that mutation of specific immunological pattern was always taking place and that, unless there was an appropriate homeostatic mechanism, clones of cells immunologically directed against body components would inevitably appear. Such cells undoubtedly do appear in pathological conditions, and on our current view represent the result of some breakdown of the homeostatic mechanism. It is convenient to use the terms "forbidden clone" or "forbidden pattern" to refer to such clones and the immunological patterns they carry.

The Reality of Somatic Mutation

Some might consider that mutation is not a legitimate concept when it is applied to the somatic cells of the body. With our present ignorance of the mechanism of differentiation, it may be an unjustified extension of the concept of mutation to apply it to cell lines within the body. To establish its validity in your minds I should like to mention two recent examples where the effect of somatic mutation can be clearly seen.

The first concerns a phenomenon described by Fraser and Short (1958) in my own country which they call fleece mosaicism in sheep. Very occasionally one observes areas of long loosely crimped fleece on a sheep which should have a uniform coat of close short wool. This is an abnormality immediately visible to any sheep-owner or stockman, and when the Australian Commonwealth Scientific and Industrial Research Organization became interested in the phenomenon it was relatively easy for them to sort over by proxy about 20 million sheep, finding in the process 30 examples of mosaicism. These sheep are of particular interest from the point of view of the extent of involvement and the way the abnormal areas are distributed over the skin. In the first place, small areas of abnormal fleece are commoner than large. Of the four animals with more than 20% involvement, one had 44% and three between 20 and 25%. Fraser and Short (1958) considered that the findings were consistent with the occurrence of a specific type of somatic mutation at one of the early stages of segmentation of the fertilized ovum. When one of the cells at the two-cell stage is involved, about 50% of the fleece is long. At the next stage there will be twice as many cells in which the mutation can occur, but when it does the effect will involve only one-quarter of the skin area, and so on for further stages of segmentation. Rough calculation indicates that there is a chance of about $1:2 \times 10^7$ per cell generation that an early embryonic cell will undergo this type of mutation and that the frequency does not vary significantly over the early stages of the segmentation of the fertilized ovum.

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It will be self-evident that a somatic mutation (or any mutation for that matter) can be recognized only when the mutating cell gives rise to an adequate and usually large number of descendants. If a mutation occurs in an adult tissue involving, say, one cell in 10^5 , there will be no way in which its existence can be recognized by any simple technique.

There is, however, one interesting possibility of detecting somatic mutation which involves only a small proportion of cells. In a human individual of AB blood group there are no circulating isoagglutinins. If, therefore, a haemopoietic cell should mutate from AB to B, any B erythrocytes produced could survive as well as the genetically correct AB cells. Atwood and Scheinberg (1958) therefore examined large volumes of AB red cells for the presence of cells inagglutinable by one of the A-agglutinating plant extracts. With much labour they were able to separate from 0.01% to 0.1% of cells which had B characters and which for reasons I need not elaborate could be regarded as resulting from a genuine somatic mutation.

I believe that these two examples have the important implications (a) that somatic cells mutate in much the same fashion as germ cells, and (b) with the same order of frequency. In other words, a tremendous amount of mutation must be going on in the body. At a rough estimate, some 10^8 of the expendable replicating cells of the body may be undergoing mutation every day. I hope that this will be accepted as justification for making use of somatic mutation in discussing the aetiology of auto-immune disease. I shall be concerned almost wholly with mutation in relation to the specificity of antibody and of immunologically competent cells (I.C.C.), but it should also be pointed out that mutation of antigenic pattern as of AB→B must always be occurring and that mutant patterns could act as antigenic stimuli in the body. This is an aspect of immunology which, to my knowledge, has never been explored and which might provide an important harvest of facts and ideas.

Our present interest, however, is with the types of mutation which could result in observable consequences or which need to be postulated to account for the facts of immuno-pathology. On our hypothesis of clonal selection observable proliferation of a mutant clone could follow several types of mutation: (1) Mutation of immunological competence to a pattern corresponding to an antigen in the body; (2) development of hypermutability necessarily involving reactivity with many body antigens; (3) block in some of the transitions between different mesenchymal cell phases where this would prevent inhibitory or destructive effects of antigenic contact; (4) loss of one or more homeostatic controls on number or concentration of cells—equivalent to premalignant or malignant change. Foretelling to some extent subsequent discussion, it is likely that all these are encountered in medicine. The first is regarded as physiological, and can result in pathological effects only when influenced by one or more of the other anomalies.

The Forbidden Clone Hypothesis

In discussing some of the auto-immune diseases, I shall make no attempt to elucidate their aetiology and pathogenesis from a consideration of the diseases themselves. Instead I shall try to elaborate the hypothesis of the forbidden clone on the basis of the clonal selection theory of immunity discussed in the first

lecture and to show how this hypothesis can be adjusted to the clinical and pathological findings.

To recapitulate the forbidden clone hypothesis: we assume that immunologically competent cells are unusually prone to mutation (Fig. 1), each such change giving rise to a new pattern corresponding in complementary fashion to a different antigenic determinant. In addition to maintaining a wide range

FIG. 1.—To illustrate the concept of an immunologically competent clone of mesenchymal cells and the changes that could be produced by mutation.

of patterns of immunological reactivity, this will inevitably mean the occasional emergence of "forbidden patterns" which can react with body components. These antigenic determinants with which forbidden patterns can react may either be directly accessible as a soluble protein in one of the body fluids or as part of the surface of a circulating cell, or they may become accessible as parts of expendable cells which are in the process of autolysis or are being otherwise disposed of. In normal individuals any forbidden clone must be eliminated, or at least prevented from proliferation. As the simplest means of providing this, we assume that, at a certain stage after primary antigenic stimulation, the cell becomes hypersensitive to destruction or inhibition by contact with a small concentration of the same antigen (see Fig. 2). On this view, the failure of homeostasis needed to allow the emergence of the forbidden clone would depend essentially on some anomaly of the processes which normally control changes of functional and morphological phase within mesenchymal cell populations.

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FIG. 2.—To illustrate a possible basis for the difference between a normal immunologically competent cell and an abnormal cell of a "forbidden" clone. The numerical values given for the concentration of antigenic determinants are purely hypothetical.

The anomaly might be either intrinsic to the cell as a result of somatic mutation or it could result from modification of the internal environment in which the cell finds itself. Under either of these circumstances, we can picture the emergence of clones reactive with normal body components. For them to be pathogenic, however, requires certain additional conditions.

In the first place, it is unnecessary to consider clones reactive against major plasma or body fluid components; these will be present in high enough concentration in the relevant environments to ensure the inhibition of all corresponding clones. No evidence of forbidden clones of this type appears to have been

FIG. 3.—To illustrate an approach to the nature of tissue damage by cells of a forbidden clone X reacting with a normally inaccessible cellular determinant X. Contact of cell with accidentally liberated X results in damage which causes more liberation of X and hence the development of a vicious circle.

found. Similar considerations probably hold also for the more readily accessible red-cell surface components. In order that a pathogenic situation should develop from the appearance of a forbidden clone of cells reactive against antigenic determinant X, we require (a) that the cell can undergo primary stimulation by X, (b) that for one of the reasons mentioned above elimination by secondary stimulation does not occur, (c) that cells of the forbidden clones can react with X under conditions which will produce local damage, and (d) that in the course of that damage more of X is produced, so allowing the initiation of a vicious circle (Fig. 3). Where the pathogenic agent is an antibody rather than an I.C.C. the corresponding requirements to (c) and (d) are (e) that the I.C.C. can find a suitable niche for proliferation in the plasma cell phase, and (f) that the antibody can react damagingly with body cells and in the process produce or render more accessible X.

The crux of the hypothesis is that a pathological situation can only develop as part of a vicious circle. The antigenic determinant *X* must be of relatively limited accessibility if the clone is to develop at all, and if lesions are to be produced the antigenic determinant must be liberated or rendered accessible in further amount as a result of the immunological damage itself. Otherwise we should expect antibody or specifically reactive cells to be "mopped up" by what *X* was available and gradually eliminated without significant pathological manifestations.

One additional possibility must always be kept in mind—that, as in every other expendable tissue of the body, mutation can occur within the mesenchymal cells, involving other aspects of the genome than the specialized patterns that we are primarily concerned with. In particular, a clone may develop an intrinsic proliferative advantage for reasons unconnected with its immunological character.

Acquired Haemolytic Anaemia

We may now discuss two important diseases from the point of view of this hypothesis. These are acquired haemolytic anaemia and disseminated lupus erythematosus.

In acquired haemolytic anaemia the antigenic determinant usually involved is not one of the standard blood group antigens. It is stated by Dacie (1954) to be common to all human red cells except those of the very rare Rh group, $-D/-D-$. The antigenic determinant has not been more closely characterized than this, and we can therefore refer to it simply as *X*. Since a Coombs test is regularly positive, we can be certain that antibody (often incomplete) is present as well as immunologically competent cells, and that the antibody can unite with *X*, which is available on the red-cell surface.

On the principle we have adopted, the effect of anti-*X* on the red cells will be to facilitate their destruction in the spleen and in the process liberate *X* in sufficiently increased amount to stimulate the proliferation of cells of clone *x*. The possibility of acquired haemolytic anaemia without circulating antibody is raised by the report of a case in a child with agammaglobulinaemia and with a negative direct and indirect Coombs test. In this case the spleen was said to show abnormally active erythrophagocytosis, raising the interesting possibility that immunologically competent cells can take on phagocytic activities. However, there seems to be no satisfactory evidence for this in normal individuals.

There are two problems of chronic acquired haemolytic anaemia that are of special interest: (1) Why are the antigens concerned obscure ones which are not those of the ABO or other easily demonstrated systems? (2) Why is splenectomy usually successful in curing or alleviating symptoms?

Some light may be thrown on both questions from Taliaferro's work on antibody response to sheep red cells in normal and splenectomized rabbits. The important feature is that, although splenectomy greatly reduces the antibody response to a single injection, the opposite effect is shown when a prolonged series of injections is given. It seems that the spleen has a special ability to accumulate antigen in sufficient amount to inhibit the production of a typical antibody against foreign cells.

This may have two implications: (1) antigen can be accumulated in the spleen from phagocytosed red cells in such a fashion that it can inhibit any forbidden clones against common antigens. Only with the "less antigenic" surface antigens is there any possibility of forbidden clones flourishing. (2) For the same reason only in the spleen will there be a sufficient amount of the rarer antigenic determinant *X* for it to act as a proliferative stimulus. The spleen, too, is a rich source of all types of lymphoid cells and contains suitable environments for the development of plasma cells.

To recapitulate, for the production of forbidden clones we need, in addition to the primary immunological mutation, (1) an accessible source of the antigenic determinant in adequate amount to act as a stimulant to proliferation but not in high enough concentration to inhibit; (2) an intrinsic (mutational) or environmental modification of the competent cells widening the normally narrow gap between proliferative and inhibitory concentrations of antigenic determinant; and (3) an adequate supply of mesenchymal cells where the antigenic determinant is present in significant quantities and the conditions are appropriate for their proliferation and conversion to plasma cells.

The only suggestions that have been made in regard to predisposing factors to acute haemolytic anaemia concern infections. There are on record a number of instances of the disease following nondescript febrile infections and appearing in the course of atypical pneumonia (associated with high cold agglutinin titres) or infectious mononucleosis. Most infections, and especially these two, have a stimulating effect on the lymphoid cells, and this may on occasion be sufficient to press a mutant clone to initiate a vicious circle of the type we have described. More subtle processes, however, may well be concerned.

Disseminated Lupus Erythematosus and the Other Collagen Diseases

The collagen diseases as exemplified by disseminated lupus erythematosus (D.L.E.) present a much more complex situation. Again we shall adopt the approach of presenting an interpretation based on the forbidden clone hypothesis and seeing how this agrees with the clinical facts rather than attempting to deduce the nature of the aetiological factors from a consideration of the disease itself.

D.L.E., then, is regarded as a condition resulting from the proliferation and pathogenic action of forbidden clones directed against a variety of antigenic determinants whose only common feature is that they are liberated as a result of tissue reaction to immunological damage. Of the almost infinite number of antigenic determinants which might fit into this requirement, the proportion active at any given time and in any given patient will vary with circumstances. This is in line with the extraordinary range and variability of symptoms in these conditions. D.L.E. is characteristically multiple in its symptomatology, and grades, virtually imperceptible, into other collagen diseases.

Fig. 4 is designed to show the interrelations of the diseases in this group to rheumatic fever, rheumatoid arthritis, and the typical collagen diseases. It has been compiled from statements in the literature in regard either to cases where there was difficulty in deciding between two or more diagnoses, or where there was clear

evidence that the condition changed from one to another, justifying a different diagnosis. A point of particular interest is the frequency with which one or other of the "malignant" forms of collagen disease may arise from what is initially diagnosable as rheumatic fever or rheumatoid arthritis. In the great majority of cases these conditions do not, of course, go on to the malignant form. The nature of the interrelationships amongst the auto-immune diseases will obviously become clear only when we can define the antigenic determinants which are involved in the various conditions. For the present we are limited to rather meagre hints from clinical pathology.

FIG. 4.—Interrelationships amongst auto-immune diseases as suggested by statements in the literature of apparent conversion of one form into another or of difficulties in differential diagnosis.

Hints from Clinical Pathology

The first possibility is an antigenic determinant which makes its appearance when the γ -globulin of an antibody becomes partly denatured on combining with its corresponding antigen. The possibility of this has been stressed by Najjar and Fisher (1955) and Milgrom *et al.* (1956). Obviously the appearance of this antigen must be a common occurrence, and on general grounds one would expect that the body would be immunologically non-responsive, subject to elimination of the corresponding clones. The findings of Milgrom *et al.*, however, indicate that quite a significant small proportion, around 1%, of apparently normal persons do have circulating antibody of this type. There is much to suggest that deposits of γ -globulin shown by fluorescent antibody staining methods in the glomeruli of the kidney and other situations in D.L.E. and related diseases represent the deposition on denatured γ -globulin of the corresponding antibody, which in its turn adds to the deposit by now becoming the antigen. Apart from playing a part in the gradual deterioration of kidney function, this antibody seems to be of relatively little direct importance. It remains to be determined, however, whether immunologically component cells of this specificity may not be concerned in helping to produce damage in areas subject to inflammatory processes.

The characteristic serological change in rheumatoid arthritis is the presence of an abnormally large globulin molecule in the circulation. In the opinion of Franklin *et al.* (1957), this represents a complex of about six normal globulin molecules with a large

normal globulin (S_{18}), the union being perhaps immunological in character. The possibility that immunologically competent cells of denatured globulin specificity are responsible for the damage in articular and periarticular areas does not seem to have been excluded. On general grounds, however, it would seem that some other substance, presumably a common product of cellular damage, is the carrier of the significant antigenic determinants that are concerned in acute arthritic manifestations.

The second region of significance is in regard to nuclear components and, in particular, to the L.E. cell factor. Findings by various authors are consistent that in D.L.E. sera there are reactive globulins which correspond to antigenic determinants present in mesenchymal cell nuclei. According to Franklin *et al.*, there are a number of different antibodies or reactive globulins of this character, one or more of which are responsible for the L.E. cell phenomenon. Included in this complex are antibodies against purified deoxyribonucleic acid (D.N.A.). It is noteworthy that these globulins are not species-specific, the antibody against D.N.A. being, for example, equally active against D.N.A. from human thymus, calf thymus, pneumococcal transforming principle, and T2 bacteriophage.

The clue to these forbidden antibodies is almost certainly to be found in the lymph nodes, which in D.L.E. are usually enlarged and contain focal areas of necrosis characterized by gross pyknosis and fragmentation of nuclei. The forbidden clone hypothesis would describe the situation as follows: In every lymph node there can be seen damaged pyknotic lymphocytes, often undergoing phagocytosis. Potential antigenic determinants of nuclear origin must be constantly available and, in the normal individual, prevented from immunological activity by the standard homeostatic machinery. Under the postulated ineffectiveness of that mechanism immunologically competent cells with any of the forbidden patterns will be enabled to proliferate. Cells of such clones now moving around the body will be apt to lodge in any regions where the relevant antigenic determinants are being liberated from damaged cells. In an otherwise healthy individual there may be virtually nowhere else than in the lymphoid tissue, and here we might well find a secondary homeostatic mechanism coming into action by the gross accumulation of antigenic determinants in the lymphoid tissues.

But with the occurrence of some minor damaging process—for example, extensive sunburn, development of hypersensitivity to penicillin, serum sickness, viral hepatitis—a focus is provided to which the pathological forbidden clones of lymphocytes and other mesenchymal cells can flock. There the damage will be accentuated by the interaction of antigen with immunologically competent cells, possibly with destruction and partial autolysis of the immunologically competent cells. (This is a probable origin of the haemotoxylin bodies.) As the process develops, both immunologically competent cells and antibodies will increase in amount and diversity, since there are undoubtedly hundreds of different antigenic determinants against which forbidden clones of cells can be developed, and which can be liberated from damaged cells of various types.

The essential feature of this hypothesis, as of the clinical picture of the severe collagen diseases, is the

extreme variability in extent and distribution of the pathological process among different organs. The whole hypothesis calls for the play of accident in determining which mutant clones will be "chosen" by the availability of antigenic determinants in the relevant lymphoid tissues at appropriate concentrations. The diseases are rare enough to suggest that somatic mutations (other than immunological) in mesenchymal cells are probably necessary for the conditions to develop. One such mutation which has already been suggested is to an insusceptibility to the inhibitory action of secondary antigenic contact. Apart from these, one could probably postulate that sooner or later all the immunological patterns would arise by immunological mutation. The variability would arise (a) by the extent to which clones were stimulated to proliferate; (b) by the degree to which plasma cell development occurred, and, on the other hand, (c) by the extent to which opportunity was available for interaction with antigenic determinants in regions not directly associated with immunological productivity; and (d) by the strength of controlling factors, especially steroid hormones.

Hints from Clinical Data

Some interesting hints may be derived from the clinical data. There is, for instance, well-authenticated information that dermatomyositis is associated with malignant disease to a significant degree. On our present approach this suggests that a spreading malignant growth will be associated with the local liberation of various cellular antigens, including in many instances antigenic determinants, especially characteristic of muscle tissue. The other predisposing conditions would have to be present, but the direction in which the build-up of proliferating forbidden clones would occur might well be determined in this fashion. A point arising from this suggestion is the indication that immunologically competent cells making contact with antigenic determinants at a local site could proliferate at a distant site—for example, spleen or thymus—provided the appropriate immunological conditions were fulfilled.

Periarteritis nodosa is probably the most difficult of all the conditions to interpret, although the characteristic lesions are to be seen to some extent in all the "collagen diseases." A clue may be found in the sex incidence—unlike the other conditions, this is more frequent in men than in women—and in the fact that it is to some extent correlated with hypertension. As in the other conditions, it appears that damage by some other process renders a tissue vulnerable to the vicious-circle effect of immune damage.

Another point of special interest is that the lesion in the Arthus reaction in the rabbit appears to be of very similar character to periarteritis nodosa. Rich and Gregory (1943) have also found that in rabbits given large doses of foreign protein vascular lesions of the same type occur, and, further, that in patients dying after having suffered severe serum sickness very similar lesions occurred. In all these conditions antigen-antibody precipitation in the tissues is a possibility, and it is usually considered that this gives rise to endothelial damage, the other changes being secondary to this.

If periarteritis nodosa is an auto-immune disease in most instances, the lesion will need to be interpreted as a vicious circle of some sort. It could be supposed that an endothelial lesion of any origin could render accessible cytoplasmic or nuclear components with which

antibody or immunologically competent cells could react damagingly and so give rise to further liberation of accessible antigenic determinant. As in all these conditions, the precise antigenic determinants involved are unknown. They might be the same as those involved in quite different types of lesion or they may be specific to an antigen present only in vascular tissues. It is of special interest that periarteritis nodosa may be localized to particular organs, notably gall-bladder and appendix. Throughout the indication is strong that two things are required; an initial vascular lesion and an immunological anomaly that allows the development of a vicious circle leading to spread of the lesion.

Questions to be Answered

If this outline of the "malignant" auto-immune diseases is correct, there are several outstanding questions to be answered: (1) What are the antigenic determinants concerned? (2) What is the anomaly in the homeostatic mechanism? (3) In what way do the "non-malignant" conditions, rheumatic fever and rheumatoid arthritis, differ from the "malignant" ones?

The Antigenic Determinants.—Some indications have already been given that (a) components of denatured γ -globulin and (b) more than one nuclear component are concerned in D.L.E. In addition, we know that a variety of red-cell determinants may be involved in haemolytic anaemia. The wide reactivity of certain sera in Gajdusek's auto-immune complement-fixation (A.I.C.F.) test suggested strongly that in some at least of the cases there was a plethora of anomalous forbidden patterns in the circulating antibody and hence by hypothesis in the clones concerned in their production. A point of particular interest was the failure of certain pathological sera to react with antigens prepared from the patient's own liver, although reactive against antigens from other individuals. It may be objected that the reactive globulins in such sera cannot legitimately be referred to as antibodies. This is true on the Haurowitz-Pauling theory of antibody production, but on the clonal selection theory an antibody is much less specifically definable. Any population of globulin molecules in a body fluid which can unite to a specifically limited range of chemical patterns can justifiably be called antibody on this theory.

Our view would be that in a florid case of D.L.E. with a high titre A.I.C.F. reaction a wide and variable range of reactive globulins with forbidden patterns can be present. It is specially significant that in most instances rat or rabbit tissues will serve as antigen in complement-fixation tests nearly or quite as effectively as human tissue emulsions.

The Anomaly in the Homeostatic Mechanism.—Some suggestions have already been made about possible anomalies in the homeostatic mechanism which would allow the emergence of forbidden clones. It is probably inappropriate to make any more detailed suggestions until more experimental evidence is available. It is to be hoped that more work will be done on hydralazine and related compounds to see whether there is an important clue to be found here. It may be significant, however, that only 10% $\pm$ of patients on hydralazine have ever developed frank signs suggestive of D.L.E.

How Do "Non-malignant" Conditions Differ from "Malignant" Ones?—Elsewhere, suggestions have been made that rheumatic fever is a manifestation of

forbidden clones of cells arising in the lymphoid tissue of the pharyngeal region. Here the homoeostatic mechanism is assumed to be broken down by the changed local conditions associated with streptococcal infection and re-established with the waning of the local infection. This is as yet no more than a working hypothesis which may stimulate experimental work toward the characterization of forbidden clones—if they exist.

Conclusion

This discussion of the auto-immune disease represents a purely theoretical study, but I believe it is important that we should have a clear theoretical background if we are to devise means to prevent or treat these conditions. One of the greatest difficulties in their study is our inability to produce analogous conditions in experimental animals. Where experimental models are not available there is perhaps greater justification for the speculative type of approach that I have used.

What I should specially like to leave with you is a sense of the existence of cellular populations within the body which, like a population of bacteria in a test-tube or rabbits in a continent, are subject to mutation, proliferation, death, and selective survival. The population dynamics of the body cells represents, I believe, the most fertile of all the broad fields of medicine that still await adequate study. Just as I completed writing these lectures, I found a new paper by Szilard (1959) putting into mathematical form a thought that has been becoming more and more insistent in my own mind—that ageing is essentially the integration of mutational damage to somatic cells. If this is true, and if I am correct in the interpretation of the pathology of immunity, and if the somatic mutational approach to cancer withstands the challenge of the virologists as I believe it will, then somatic mutation as an aetiological consideration may come to dominate the whole of medicine in so far as it is concerned with the waning half of human life.

The approach is an unpopular one—mutations are irreversible and there is no presently conceivable way in which the process can be prevented. Curative approaches, too, must be indirect and largely empirical. Medical science, however, is growing up, and I think it is time that we stopped fostering the naive expectation of the public that genetic anomalies, including feeble-mindedness, cancer, the degenerative disabilities of age, and death itself, will all eventually be overcome as surely as we can deal with pneumococcal pneumonia or malaria. There will always be much that we can do as doctors, but we must base our expectations upon facts and leave a belief in miracles to others.

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KARTAGENER'S SYNDROME WITH FIBROCYSTIC DISEASE

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Situs inversus has been recognized from antiquity; among the ancients Aristotle is said to have noticed two cases of transposed organs in animals. The Renaissance and its aftermath saw a renewed interest in anatomy; Fabricius, one of the successors of Vesalius at Padua and among whose pupils was William Harvey, described a case of reversed liver and spleen in the human in 1660; and Petrius Servius, in 1615, recorded a case of transplantation of the viscera (Lineback, 1920; Sherk, 1922). It was not until the early nineteenth century that the condition was first diagnosed clinically. By the latter part of the century such a diagnosis could be confirmed with accuracy by the newly discovered roentgen rays. Over 1,000 cases of this abnormality have now been recorded, and it has been estimated that it occurs as often as one case in approximately 1,400 of the general population (Johnson, 1949). It is not incompatible with normal health, however, and it is often related how Elisha Bartlett, a distinguished physician of his day, lived a normal life-span with complete transposition of the viscera. The condition itself may be complete or partial, when it may be limited to the abdominal or thoracic organs alone. It is often associated with numerous other congenital abnormalities (see review by Wood and Blalock, 1940).

Kartagener (1933) described a group of patients with bronchiectasis who had situs inversus, recognized in the main by the discovery of dextrocardia; his cases also had abnormalities of the paranasal sinuses. It has become general experience that the incidence of bronchiectasis and sinusitis in patients with rotational abnormalities is greater than that noticed in the general population; for instance, Adams and Churchill (1937) found that 21.7% of a series of patients with situs inversus studied by them had bronchiectasis; the comparable incidence of bronchiectasis in the general hospital population was 0.36%. In view of the association of bronchiectasis with the obvious congenital abnormalities in the situs inversus cases, the hypothesis has been advanced that this is one type of true congenital bronchiectasis, with cystic changes in the lung as a result of dissociated tissue held to be primitive foregut tissue occurring within the lung bud. It is the opinion of others, however, that the bronchiectasis is acquired from infected sinuses which are congenitally malformed. It is our purpose to record a further case of this syndrome in a patient in whom it seemed likely that the bronchiectasis and other clinical failures were associated with fibrocystic disease of the pancreas.

Case History

A man aged 20 woke on the morning of March 19, 1957, with epigastric pain. This at first came in spasms and was