Papers and Originals

Contribution of Modern Immunological Concepts to an Understanding of Diseases of the Skin*

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Contribution of Dermatology to Modern Immunology

In a discussion of the contribution of modern immunological concepts to an understanding of diseases of the skin one cannot help paying tribute to those dermatologists who contributed so much to the broadening of the concepts of immunology beyond those imposed by a simple study of the protection of the body from infecting organisms. It was this approach which was the forerunner of our modern concepts of immunology, whereby we accept that there are few branches of medicine which are not affected by immunological thought.

Ten years before von Pirquet (1906) gave the term "allergy" to an "altered capacity to react" to a bacterial or viral antigen, Jadassohn (1896) described increased reactivity to a simple metal contact agent, mercury. Following Jadassohn's description, research into the mechanism of contact sensitivity progressed in parallel with that into other allergic states. Cash (1911) produced contact sensitivity in himself to East Indian satin-wood, and Cranston Low in 1924 sensitized eight individuals to *Primula obconica*. Bloch and Steiner-Wourlich (1930) were the first to show that contact sensitivity could be produced in experimental animals. But it was not until this major breakthrough had been made that contact sensitivity became a tool in the experimental study of what we now know as "specific cell-mediated immunity." The experiments of Bruno Bloch and his team stimulated Landsteiner, the greatest experimental immunologist of his age, to set his team to study the model of action of this type of allergic reaction and demonstrate that sensitivity could not be transferred from animal to animal by serum but could be transferred by cells of the lymphoid series (Landsteiner and Chase, 1942).

In the same way as the foundations of our knowledge of cell-mediated immunity can be found in the studies of dermatologists, one can also find in their observations the foundations of the study of immunological tolerance. The dermatologist has a considerable advantage over his colleagues in internal medicine or surgery. Direct observation of the lesions on the skin as they develop and regress is possible in a way that would be unthinkable in any other tissues. It is thus not unnatural that so many fundamental immunological subjects were studied by dermatologists, often two or three decades before their study and definition by experimental biologists or physicians. The first observation of immunological tolerance was made in man by Frei (1928a, 1928b). Frei was able to sensitize humans to neoarsphenamine by intradermal injection. He found, however, that he could not sensitize people who had had previous intravenous injections of neoarsphenamine for the treatment of syphilis. These experiments were performed later in guinea-pigs by Sulzberger

(1929) and by Chase (1963). Meanwhile Chase (1946) had found that feeding 2,4-dinitrochlorobenzene by mouth regularly led to the tolerant state, so that guinea-pigs failed to develop contact sensitivity when sensitization was attempted at a later date.

A further example whereby a study of skin lesions has led to the opening of a new field in immunology has been the study of vaccinia gangrenosa. Investigation of this condition has led to much of our modern knowledge of immunity deficiency states in man.

These fields of modern immunological research—cell-mediated immunity, immunological tolerance, and immunity deficiency states—are perhaps three of the most important aspects of current immunological research. Research into the first two has led to major advances in transplantation immunity and through it to transplantation surgery. The third aspect is now one of the most widely studied subjects in paediatrics.

Having paid tribute to the contribution of dermatology to modern immunological thought, one must now ask how immunology can contribute to dermatology in the future. For such a lecture must not be a catalogue of past achievements but a stimulus to future research and development.

Immunological Processes in Disease

Fundamentally, immunological processes involve the recognition of something that is foreign to ourselves, and is thus not part of "self" from ourselves. The phase of recognition is then followed by the rejection from our bodies of that which is foreign. We use the term antigen to describe that which we recognize immunologically as foreign, whether a micro-organism, cancer cells, transplanted tissue, or our own tissues which have been altered by conjugation with a simple chemical grouping, such as 2,4-dinitrochlorobenzene.

Immunological reactions are specific in that the body can recognize chemical groupings differing in size from simple chemicals (haptens) such as 2,4-dinitrochlorobenzene bound to carrier proteins, or to a wider determinant consisting of the hapten and the adjacent part of the carrier protein molecule. Polysaccharides can also be recognized as antigenic; however, they have to have a molecular weight of as high as 600,000, whereas to be antigenic a foreign peptide need be no larger than 6,000 M.W. Lipids are not antigenic unless forming a complex with proteins or polysaccharides. Following recognition an antigen may be rejected by two different immunological processes. The first involves immunoglobulin molecules present in the plasma which carry specific antigen recognition sites. These are referred to as antibodies. The second means is by specific cell-mediated processes. In this process the active cell is the lymphocyte, which is believed to carry specific antigen recognition sites analogous to those found on the immunoglobulin molecule.

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Reactions in the skin due to immunoglobulin molecules take a shorter time to develop and resolve quicker than those due to cell-mediated immunological processes. This could be expected owing to the greater ease of immunoglobulin-antigen interaction. The immune complexes formed between antigen and immunoglobulin would appear in many cases to diffuse away or be inactivated more rapidly from the reaction site than those formed between lymphocyte and antigen. Thus reactions in the skin between antibody and antigen are referred to as "immediate-type hypersensitivity," while those due to the interaction between specifically sensitized lymphocytes and antigens cause "delayed-type hypersensitivity" reactions. Immediate hypersensitivity reactions in the skin may be due to two different types of immunoglobulin molecule. The IgE molecule sticks powerfully to tissue surfaces, including those in the skin, and is thus often referred to as "skin-sensitizing" antibody. This molecule causes the anaphylactic type of allergic reactions as rapidly as 15 minutes after antigen-antibody contact. The result of such a reaction is the release of vasoactive amines and other pharmacological agents from mast cells, and is one of the causes of urticaria.

Immune complexes containing IgG molecules do not stick so rapidly to tissue surfaces. They get deposited in or interact across the walls of small blood vessels, causing an "Arthus reaction" which is one of the causes of an allergic vasculitis, taking four to eight hours to develop and resolving more slowly than true allergic urticarial reactions. Delayed hypersensitivity reactions such as contact sensitivity to simple chemicals take 24-48 hours to develop and may take as long as a week to resolve. Whereas immunoglobulins have been known for many years to be involved in the defence against a wide range of bacteria, the importance of cell-mediated immunological processes is only just becoming recognized. It is now known that cell-mediated immune processes are necessary for the defence of the body against mycobacteria, protozoa, fungi, and a wide range of viruses. It is possible that cell-mediated immunity is necessary for defence against many other organisms as well.

In the field of contact sensitivity, modern immunological thought has helped us to understand more fully some of the phenomena that have been known by clinical dermatologists for many years. One of these is the observation that some people do not get sensitized though they have received an identical or even greater exposure to the allergen than others who do become sensitized. In experiments using inbred strains of guinea-pigs it was found that one strain could be sensitized to develop contact sensitivity to potassium dichromate and beryllium fluoride and not to mercuric chloride, whereas another strain could be sensitized to mercuric chloride but not to potassium dichromate or beryllium fluoride. Moreover, the ability of guinea-pigs to become sensitized was found to be inherited as an autosomal dominant characteristic (Polák, Barnes, and Turk, 1968). Another phenomenon which became amenable to investigation was that of the generalized eruption, associated with contact sensitivity or infective processes in the skin, which some people have postulated as being due to an autosensitization to breakdown products of skin. Sulzberger (1940) showed that secondary eruptions associated with fungus infections of the skin could be reproduced by systemic absorption of the fungus. Moreover, generalized eruptions can be produced in experimental animals sensitive to contact agents by systemic absorption of the contact agent, either following intravenous injection or after absorption from an abraded skin site (Frey, de Weck, and Geleick, 1964; Polák and Turk, 1968).

Finally, light may be thrown on the nature of fixed drug eruptions by investigation of the "flare up" of old contact-testing sites in the skin following the systemic injection of the chemical. Such a flare up can be produced regularly in experimental animals up to three months after the last contact reaction at a time when there is no histological evidence of the

residual reaction. These flare ups differ from the contact reactions in that they develop within four hours of the systemic injection and the reaction consists of a perivascular polymorphonuclear leucocyte infiltration of the dermis, rather than a mononuclear cell reaction as is found in the original contact reaction. Evidence is accumulating that these flare-up reactions are not due to a cell-mediated immune process similar to that which is responsible for contact sensitivity, but are due to the local production of humoral antibody produced by immunologically active cells left over at the original contact site. These cells must remain fixed at the old skin reaction site for long periods of time and are probably present in very low concentration, as they cannot be detected by conventional histological methods (Polák and Turk, 1968).

Disease processes can be caused either by hyperactivity of the body against an antigen producing an allergic reaction or by a defect in the body's immunological processes causing micro-organisms to spread throughout the body or an inability to eliminate new clones of neoplastic cells as they develop.

New Classification of Immunological Disorders of Skin

Having determined that disease can be caused by what von Pirquet (1906) described as "an altered capacity to react," which one might now call increased immunological activity, one may also add that disease can be caused by decreased immunological activity (see Table). Such increased or

Examples of Immunological Diseases

	Specific	Non-specific
Increased	(a) Cell-mediated Tuberculoid leprosy Contact hypersensitivity (b) Humoral antibody (i) IgE Anaphylaxis Urticaria, Asthma, etc. (ii) IgG Immune complex diseases Chronic serum sickness Erythema nodosum leprosum Glomerulonephritis	? Atopic dermatitis —High IgE and reagins —High IgG
Deficiency	Cell-mediated (i) Lepromatous leprosy (ii) Diffuse cutaneous leishmaniasis (iii) Mucocutaneous candidiasis	(a) Neonatal thymus agenesis (b) Defective immunoglobulin synthesis (c) Combined Immunological deficiency syndrome

decreased immunological reactivity may be specific to a particular antigen or micro-organism or may be the result of a generalized non-specific ability to over-react or failure to react in a particular way to any antigen with which the body might come into contact.

Disorders of the skin due to specific hyperreactivity to a particular antigen involving cell-mediated immune processes include lupus vulgaris and tuberculoid leprosy, where the antigen is mycobacterial, and chemical contact sensitivity, the cause of a considerable amount of industrial morbidity in a modern technological society (see Table). Specific increased reaction due to humoral antibody of the IgE type causes urticarial reactions in the skin, whereas a specific disorder of the skin of the "immune complex" or Arthus type involving IgG antibody can be shown to underlie erythema nodosum leprosum (Wemambu, Turk, Waters, and Rees, 1969) and probably other types of allergic vasculitis (Miescher, Paronetto, and Koffler, 1966).

Specific immunity deficiency diseases include lepromatous leprosy (Turk and Waters, 1969), diffuse cutaneous leishmaniasis (Bryceson, 1969), and mucocutaneous candidiasis. Non-specific immunity deficiency diseases may be the result of a defect in cell-mediated immunity, only as a result of neonatal thymus agenesis (DiGeorge or Nézélof syndrome), or a relative pure defect in immunoglobulin synthesis. An hereditary combined immunity deficiency syndrome, however, also

occurs in which there is a defect in both cell-mediated immunity and immunoglobulin synthesis. Immunity deficiency syndromes also occur in later life and can be said to be acquired if there is no known primary aetiology or secondary to a wide range of other disorders. Secondary defects in the circulating level of immunoglobulins can be (a) physiological, (b) catabolic, (c) due to bone marrow disorders, (d) due to toxic factors, or (e) associated with primary reticulo-endothelial neoplasms.

Secondary defects in cell-mediated immunity occur when the areas of lymphoid tissue in which the mobile pool of small lymphocytes involved in cell-mediated immune processes get infiltrated with pathological tissue. This occurs in diseases such as the Wiskott-Aldrich syndrome, lepromatous leprosy, Hodgkin's disease, and other primary diseases of the reticuloendothelial system. In these conditions, however, the inability to develop cell-mediated immune processes is partial in that the patients may fail to be sensitized to dinitrochlorobenzene, but only terminally may show a defect in cellular immunity to infecting organisms. Non-specific deficiencies in cell-mediated immunity in leprosy and Hodgkin's disease are also associated with a failure of lymphocytes to react in vitro to antigens and non-specific mitogens. In some cases this has been associated with the presence of an antilymphocyte factor in the plasma (Bullock and Fasal, 1968; Nelson and Waters, personal communication).

Atopic Dermatitis

Atopic dermatitis is an example of a disease in which there is a non-specific increase in reactivity against ubiquitous external antigens. Non-specific reactivity to intrinsic antigens results in an increase in the level of autoantibodies to thyroid antigens, nuclear antigens, antigens on immunoglobulin molecules, and tissue antigens in old age and chronic infections such as tuberculosis, leprosy, syphilis, kala-azar, and malaria. There is no evidence, however, that these antibodies can be the direct cause of lesions in the tissues.

Children with atopic dermatitis tend to be predisposed to develop anaphylactic phenomena such as asthma to a wide range of antigens in adolescence and early adult life. Patients with this disease readily develop skin sensitizing (anaphylactic) antibodies in their serum to a wide range of different antigens. They have a high level of circulating IgE and IgG immunoglobulins (Juhlin, Johansson, Bennich, Hogman, and Thyresson, 1969; Varelzidis, Wilson, Meara, and Turk, 1966). IgE levels return to normal when the patients have been free from eczema for at least two years (Johansson and Juhlin, 1970).

Raised immunoglobulin levels in atopic dermatitis are associated with some degree of lowered cell-mediated immunity in that the patients may have a lower resistance to the viruses of herpes simplex and vaccinia and are readily susceptible to secondary infection. The role that this non-specific rise in IgE antibodies, capable of reacting with a wide range of different allergens, has on the mechanism of the skin lesions is difficult to assess. In the first place the condition is eczematous and not urticarial. Histologically there is a vascular dilatation and pronounced infiltration of the dermis with lymphocytes, again reminiscent of a cell-mediated rather than an urticarial condition. Finally there is the observation that clinical atopic dermatitis can occur in children with low levels of circulating immunoglobulins who were not found to develop skin sensitizing antibodies.

Though little is known about the aetiology of atopic eczema, the evidence to hand seems to indicate that this syndrome is associated with a number of functional abnormalities of the antibody-producing mechanism, probably of hereditary origin. The high incidence of skin sensitizing antibodies and the high incidence of patients with a raised

level of IgE and IgG immunoglobulins in the serum, associated with a marked susceptibility to infection, would indicate that there could be a functional overproduction of certain antibodies with a reduced production of other types of antibodies. This hypothesis that atopic dermatitis is the result of a malfunctioning immunological mechanism is confirmed by the regular occurrence of this condition in the Wiskott-Aldrich syndrome. The Wiskott-Aldrich syndrome, which consists of eczema, thrombocytopenia, and frequent severe infections, is a sex-linked recessive disease in which there is a high mortality from infection. Though normal levels of immunoglobulins are found in the serum, the patients behave clinically as though they were defective in immunoglobulins in that they are unable to produce antibodies regularly, and frequently have low levels of isohaemagglutinins in the serum. If the cause of this disease is due to abnormal immunological functioning, a similar failure might well be the cause of atopic eczema in other children.

Spectral Forms in Infectious Diseases

The clinical response of a patient to infection with a micro-organism depends as much to the host's response to that organism as to any direct pathogenic effect of the organism. Many organisms are pathogenic simply as a function of their invasiveness and ability to proliferate within the host. These organisms do not produce external toxins which are directly damaging to the host, and the resultant disease process can be attributed to the host's immunological response or lack of immunological response to the invading organism. Thus the form that the disease takes is due to the position on a spectrum of the host's response, varying from the one extreme of hyperreactivity to the antigens carried by the parasites, bacteria, or fungi to the other extreme in which there is a complete lack of host reaction, as a result of which the organisms can proliferate within the body in an uncontrolled manner.

Leprosy

Much of our knowledge of the immunological spectrum of infectious diseases has come from a study of leprosy. As a result of this analogy has been drawn to spectral forms of diseases due to other micro-organisms such as *Leishmania* spp. and candida. These organisms need cell-mediated immune processes for their elimination from the body, and can spread throughout the tissues despite high levels of circulating humoral antibody. The spectrum of disease in leprosy was originally classified by the realization that there was a histological spectrum in this disease (Ridley and Jopling, 1966).

In this study a correlation was made between the clinical features of the patients and the histological appearance of skin biopsies. In tuberculoid leprosy at one end of the spectrum there was marked lymphocytic infiltration of the tissues, and *Mycobacterium leprae* could be found with difficulty if at all. In lepromatous leprosy at the other end of the spectrum lymphocytic infiltration was virtually absent and *M. leprae* can be seen to grow in an uncontrolled manner within macrophages throughout the tissues. Between these two polar forms of the disease within what is known clinically as the "borderline" form of leprosy there is a spectrum of appearances in which the amount of *M. leprae* found in the tissues is inversely proportional to the degree of lymphocytic infiltration. Micro-organisms such as *M. leprae*, *Leishmania* spp., and candida need cell-mediated immune processes for their elimination from the tissues. Lepromatous leprosy is thus an example of a specific immunity deficiency disease, whereas in tuberculoid leprosy the disease state is due to a specific hyperreactivity of cell-mediated immune processes.

There is much evidence that the immunity deficiency state in lepromatous leprosy is a host-determined characteristic that is possessed by a fixed proportion of people everywhere and is probably genetically determined (Newell, 1966). Nevertheless, despite the ability to induce a disease resembling lepromatous leprosy in experimental animals in which a general depression of cell-mediated immunity has been produced by adolescent thymectomy followed by deep x-ray irradiation (Rees, Waters, Weddell, and Palmer, 1967), it is likely that the deficiency in cell-mediated immunity in man is initially specifically directed towards *M. leprae* itself. In 50% of patients, however, there is also some evidence of a non-specific suppression of cell-mediated immunity. This can be demonstrated by an inability to develop contact sensitivity to 2,4-dinitrochlorobenzene and an increased retention of skin grafts. There is also some evidence of decreased lymphocyte function in that there is a decreased ability of these cells to be transformed into "blast" cells by non-specific mitogens such as phytohaemagglutinin. All patients with lepromatous leprosy, however, can be induced to produce delayed hypersensitivity to an extremely strong antigen such as keyhole-limpet haemocyanin (Turk and Waters, 1969), indicating that deficiency in cell-mediated immunity is far from complete. It may be that the degree of non-specific loss of cell-mediated immunity is related to the extent to which the lymphoid tissue of the body is replaced by granulomatous tissue, as has been suggested in Hodgkin's disease (Brown *et al.*, 1967; Turk and Waters, 1968). Another reason may be the presence of a serum or plasma factor which decreases the ability of normal lymphocytes to be transformed into blast cells.

Circulating Antibodies

Despite an inability to eliminate these organisms by cell-mediated immune processes, patients with lepromatous leprosy have a high level of circulating antimycobacterial antibodies in their serum. As a result of this they develop lesions in the skin due to the deposition of immune complexes containing immunoglobulin, complement, and soluble mycobacterial antigens (Wemambu *et al.*, 1969). These lesions histologically take the form of a cutaneous vasculitis with marked perivascular polymorphonuclear leucocyte infiltration. Clinically these lesions may take on a number of patterns depending on the depth in the skin at which the lesion occurs. The lesions are usually erythematous and indurated, but may resemble erythema multiforme or, in more severe cases, be frankly petechial. This condition—erythema nodosum leprosum—can be found to develop in up to 50% of patients with lepromatous leprosy during the first year of treatment with sulphones, at a time when the micro-organisms are being killed by the drug and free soluble antigen is being released in large amounts into the tissues.

Patients with leprosy do not necessarily stay at the same point on the immunological spectrum. The disease, especially in the borderline state, may be extremely unstable. Thus without treatment a patient at the tuberculoid side of borderline may lose immunity and move to a more lepromatous condition, or a patient who is in the borderline state may develop a condition that is frankly lepromatous. Similarly, on sulphone therapy the patient may regain cellular immunity due to the fall in the antigenic load, as a result of which the tolerant state may be lost. Under these conditions the patients move more towards the tuberculoid end of the spectrum and develop multiple tuberculoid-type lesions, known by leprologists as reversal reactions. These acute lesions in the skin are due to a heightened state of cell-mediated immunity and have many of the appearances of typical delayed hypersensitivity reactions, in marked contrast to erythema nodosum leprosum, which is a clinical manifestation of the Arthus phenomenon.

Leishmaniasis

A similar immunological spectrum in cutaneous leishmaniasis has been described by Bryceson (1969). In this spectrum the more common oriental sore takes an intermediate position similar to that of borderline leprosy in the leprosy spectrum. The equivalent of lepromatous leprosy is diffuse cutaneous leishmaniasis, which is both clinically and histologically associated with a specific loss of cell-mediated immunity. In this condition lymphocytes are scanty or absent and the parasites grow in the skin in an apparently uncontrolled manner within macrophages. The delayed hypersensitivity skin test with leishmanin is negative, indicating a failure of cell-mediated immunity to leishmanial antigens. A proportion of these patients, however, develop a degree of non-specific failure of cell-mediated immunity in that they cannot be sensitized with 2,4-dinitrochlorobenzene. The rare form of lupoid leishmaniasis represents the tuberculoid end of the spectrum. In relapses after treatment patients with diffuse cutaneous leishmaniasis may swing across to the tuberculoid side of the spectrum and develop lesions in which epithelioid cells, often containing parasites, are mixed with or surrounded by lymphocytes, forming "tubercles." It is probable that kala-azar is another form of immunity deficiency state, but in this case the organism belongs to a different species of *Leishmania* than that causing cutaneous leishmaniasis, and can be shown to be antigenically distinct. Patients with this disease are also leishmanin-negative.

A similar immunological spectrum can be found in diseases due to infection with yeasts. One of these which has been studied extensively in Brazil is South American blastomycosis. It has been found that patients with the benign form of this disease, which has the potential of self-healing, can show delayed hypersensitivity reactions to paracoccidiomycin, an extract of antigens from the infecting organism. Like patients with tuberculoid leprosy they also have a low incidence of circulating antibody against the organism. Nevertheless, in the disseminated form of the disease which recurs even after repeated courses with antibiotics and chemotherapeutic agents, the patients do not have the capacity to show delayed hypersensitivity reactions to paracoccidiomycin, indicating that they have lost cell-mediated immunity against the organism. Like patients with lepromatous leprosy, they have a high level of precipitating antibodies against antigens of the infecting organism (Da Silva Lacaz, 1967).

A Ubiquitous Organism

A more common disease in Western Europe and North America which develops as a result of impaired cellular immunity is that caused by *Candida*. This organism is ubiquitous in the community. Sporadic cases, however, are being described where the organism causes a continuous mucocutaneous infection or even a pulmonary disease similar to that seen in South American blastomycosis. Most of these patients cannot produce delayed hypersensitivity to extracts of candida, indicating a specific failure of cellular immunity against the organism. In some of these patients the failure of cell-mediated immunity may be secondary to an underlying endocrine upset, reminiscent of the immunological defects found in congenital dwarf mice (Pierpaoli, Baroni, Fabris, and Sorkin, 1969), which have a deficiency of thymus function that can be reversed by treatment with growth hormone and thyroxine.

Varying degrees of non-specific failure of cell-mediated immunity have been described in these patients. In some of them there is a relative deficiency of cell-mediated immunity in that the lymphocytes show an impaired ability to be transformed by non-specific mitogens *in vitro*. In others the lymphocytes can be transformed normally by non-specific mitogens and even by extracts of candida, but fail to produce

the pharmacological agents *in vitro* which are believed to be involved in cell-mediated immune reactions (Chilgren, Meuwissen, Quie, Good, and Hong, 1969). In others there was a failure of the lymphocytes to be transformed by candida antigen *in vitro*, though they could respond normally to non-specific mitogens. Thus failure of cell-mediated immunity to candida may in some cases be the result of a general non-specific ability of the patient, often a child, to develop cell-mediated immunity. In others failure to eliminate the organism may be a failure of specific reactivity against the organism at a number of different levels, from that of immunological recognition to the final ability of the lymphocyte to produce pharmacological agents associated with the manifestation of cell-mediated immune reactions.

Possible Cell-mediated Immunity in Syphilis

One might end this section with a discussion of the possible role of cell-mediated immune processes in the development of the early manifestations of syphilis. In leprosy, cutaneous leishmaniasis, and South American blastomycosis we are dealing with diseases in which there is what might be called a horizontal immunological spectrum. The position of the patient on the spectrum at any particular time is related to the state of cell-mediated immunity against the organism in certain stages of the disease. If the antigen load increases, cell-mediated immunity may become lost by a process of immunological tolerance. If the antigen load is decreased, however, cell-mediated immune reactions against the organism or its antigens may be increased.

In infections with *Treponema pallidum* it may be that we are dealing with a vertical spectrum in which disease runs progressively in one direction, rather than having the potential to swing from side to side according to the level of antigen in the body. The finding of a depression of lymphocyte function, as shown by an impaired ability of these cells to be transformed into blast cells by mitogens, could indicate a non-specific reduction in cellular immunity during the early stages of this disease. The association of this impairment of lymphocyte function in secondary syphilis with a soluble factor in the plasma (Levene, Turk, Wright, and Grimble, 1969) suggested that this type of impaired lymphocyte function could be a common factor in a number of chronic infectious diseases. The nature of this circulating soluble antilymphocyte factor, present in plasma of both leprosy and syphilis patients, is not known. It could be a product of bacterial metabolism, or it might be produced by the host as a result of bacterial stimulation. In both of these diseases there is an increased incidence of anti-tissue autoantibodies. Could this factor be an antilymphocytic autoantibody? This relative impairment of lymphocyte transformation in active early syphilis may be related to the finding of Festenstein, Abrahams, and Bockkenheuser (1967) of a partial depletion of lymphocytes in the spleens of neonatal rabbits infected with *T. pallidum*. Dr. David Wright and I have seen similar appearances in the spleens of human babies who died with congenital syphilis in the first year of life. It may therefore be due to the direct action of treponemal metabolites in the circulation.

With these findings in mind it is conceivable that immunity in syphilis is cell-mediated rather than dependent on humoral antibody. Following infection with the organism there is a depression of cell-mediated immunity, as a result of which the organism proliferates at first locally and then throughout the body. When humoral antibody is produced it reacts with antigen, either in the organism or in a soluble form. At first there is a reaction at the site of maximum antigen deposition. It is perhaps no coincidence that histologically the primary chancre is a vasculitis with marked perivascular polymorphonuclear leucocyte infiltration, resembling an Arthus reaction. The next stage of the disease, that of sec-

ondary syphilis, has many of the features of an immune complex disease with nephritis, iridocyclitis, arthritis, as well as the typical rash. Then the skin lesions change character and become "tuberculoid," as if cell-mediated immunity had in some way recovered. Finally, after waxing and waning the lesions disappear, and it is only many years later that the tertiary manifestations develop, and then only in a proportion of patients infected.

If elimination of the organism could be shown to be dependent on cell-mediated immune processes and the early allergic manifestations on humoral antibody mechanism, the progressive regular pattern of the disease in syphilis might be explained logically. I have used the term "vertical spectrum" to describe this progressive loss and regain of cell-mediated immunity associated at first with a "rebound phenomenon" before it settles back at its normal level. This differs from what I call a horizontal spectrum by its progressive predictable direction. In infectious diseases with a horizontal spectrum the disease is found in two polar forms—one in which cell-mediated immunity is absent, the other in which it is exaggerated and the disease can oscillate between these two poles. In a vertical spectral disease the disease takes a predictable course from failure of cellular immunity to exaggerated cellular immunity, to reach a final stage in which a balance is reached between the organism and the host's defences. Perhaps the development of tertiary syphilis in later life is due to some upset in this state of balance due to extrinsic factors or the known impairment of cellular immunity which comes with age.

Hypothesis, however, is no more than a stimulus to further research and has value only as such. Therefore I hope that this hypothesis will stimulate further research into the mechanism of skin diseases due to infectious agents.

Autoimmune Phenomena in Skin Diseases

The demonstration of autoantibodies in the serum of patients with pemphigus by Beutner and Jordan in 1964, that would react with material in the intercellular spaces of stratified squamous epithelium, raised great interest and high hopes in the dermatological world. As a result of this a considerable amount of work has been done on autoimmune phenomena. Nevertheless, on reviewing the immense amount of literature accumulating, one cannot but come to the conclusion that the demonstration of these autoimmune phenomena has done little to increase our understanding of the various skin diseases in which they have been demonstrated. The general impression that is obtained is that these autoantibodies develop as a result of the unmasking of a hidden antigen by some primary non-immunological pathological process. A recent report of interest has been that of Tan and Stoughton (1969) who found that D.N.A. could be made immunogenic by ultraviolet irradiation, suggesting that an allergic reaction to D.N.A. altered by ultraviolet light might underlie certain types of photosensitivity in the skin. Nevertheless, evidence for an allergic basis for such reactions in man so far is very slender. One cannot fail to feel that this approach to the mechanism of skin diseases has been a disappointing one, and that more knowledge will be obtained in the future by studying immunological reactions involving extrinsic rather than intrinsic antigens.

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Duodenal Ulcer and Recurrent Dyspepsia

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Summary: A survey of recurrent indigestion in four general practices (19,619 patients) showed a wide range of dyspeptic complaints. Of these 82 (4.2 per 1,000) already had a proved ulcer and 144 (7.3 per 1,000) had symptoms suggesting a duodenal ulcer and had either not been investigated or had previously had a normal barium meal. A duodenal ulcer was found radiologically in half the men (46 out of 95) but in only 16% of the women (8 out of 49). In 11 (25%) of the 46 men shown to have an ulcer a barium meal had been previously reported as normal. Evidence is put forward that ulcer symptoms in the large residue of patients with a normal barium meal (38 men, 29 women) were produced by a primary duodenal condition (duodenitis) of which ulcer was one complication.

Introduction

In general practice the spectrum of dyspeptic complaints is very wide. On the one hand are the clearly defined and well-documented pathological conditions often seen in hospital; on the other are the many cases of minor recurrent indigestion rarely reported to the doctor. The great variations in symptom severity and radiological techniques have led to difficulties in estimating both prevalence and aetiology. Consequently there has been a confusing multiplicity of names—some clinical, others implying a disorder as yet unproved. Doll and Avery Jones (1951) called the condition of dyspepsia with apparently normal barium-meal appearances "presumptive peptic ulcer"; other terms proposed have been pseudo-ulcer (Barfred, 1958), duodenitis (Beck *et al.*, 1965), and non-ulcer dyspepsia (Edwards and Coghill, 1968).

We were especially interested in those patients with a history suggesting duodenal ulcer in whom barium studies showed no abnormality. We correlated the evidence of radiology, ABO blood group, ABH secretor status, and serum pepsinogen with clinical findings in an attempt to provide basic information about those problems of incidence,

aetiology, and management that make the handling of these patients difficult in general practice.

Methods and Materials

Four practices in north-east England (three urban, one rural) involving nine doctors and 19,619 National Health Service patients took part in the project. Diagnostic indexes were kept by each practice, thus every patient reporting with recurrent or chronic indigestion could be identified and later questioned. This technique allowed the first phase of case selection to be carried out on a routine basis without observer bias and ensured inclusion of the complete spectrum of recurrent dyspepsia encountered by the doctors.

Ulcer-type Dyspepsia.—This clinical label is used for those patients with apparently normal barium-meal appearances and the following symptom triad: periodicity involving two or more attacks of upper abdominal pain during the previous two years; combined duration of such attacks of six or more days; and relief of this pain by food, milk, or alkalis. Throughout this paper duodenal ulcer, gastric ulcer, and chronic cholecystitis refer to radiologically diagnosed cases unless otherwise stated. Reflux oesophagitis refers to all cases in which oesophageal reflux or hiatus hernia has been demonstrated by x-ray examination.

Nervous dyspepsia (including functional gastritis) refers to all cases of ill-defined recurrent dyspepsia in which the symptom triad was incomplete.

Between 1 January and 30 September 1966 351 patients reported to the practices with recurrent dyspepsia of varying origin. These patients were later contacted and the following procedures instigated:

A standardized clinical history, examination, and radiological investigation were arranged. Blood and saliva were taken for three purposes: (a) ABO group; Aird *et al.* (1954) showed that the incidence of duodenal ulcer was high in group O patients. (b) ABH secretor status; Clarke *et al.* (1956) showed that the incidence of duodenal ulcer was high in non-secretors—that is, patients who do not secrete blood group antigens in their saliva. (c) Serum pepsinogen; Spiro *et al.* (1956) and Mirsky *et al.* (1952) showed that serum pepsinogen was related to a high gastric acid secretion and was raised in duodenal ulceration. The method of estimation was that of Hanley (1964).

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