AUTO-IMMUNE MECHANISMS IN DERMATOLOGY

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Auto-immunity or auto-allergy is the sensitization of the body to constituents of its own tissues. On the other hand, conventional allergy is a state of sensitivity of the body to a usually recognizable extrinsic antigen. Normally the body does not become sensitized to its own tissues as the immunologically competent lymphoid cells which are responsible for antibody production are capable of differentiating the "self" from the "non self" antigens[1,2,3]. This is believed to be the result of the recognition by the body of its cellular constituents early in its existence.

Normally any cells which possess immunological reactivity for "self" antigens will be rendered non functional either by genetic repression, inhibition or by actual destruction of these cells.[4] So auto-immunity is basically due to a fault in the recognition of or tolerance for "self" constituents.

Broadly speaking auto-immune diseases belong to two main categories.[5,6]

(1) Those due to alterations or inherent characteristic of the antigenic tissue, and

(2) Those due to alterations or inherent characteristics of the antibody producing cell.

With regard to the first category auto-immune antibodies can be produced under the following circumstances.

(1) *Unaltered self tissue as Antigenic :*

Keratin and distal epidermal cells, lens, thyroid, testes and brain tissues, which are relatively isolated from lymphatic and vascular channels; if these tissues under abnormal conditions gain access to lymphatic channels and consequently to the immunological system they can in a sense be considered "foreign" to the host, thereby stimulating antibody production.

(2) *Altered self Antigens :*

In some conditions, auto-immunization occurs against altered self components. Alterations of the host's own tissue can be produced by such factors as infection, drugs, chemical agents, physical agents, etc. In these conditions the altered antigen is similar but not identical to the "self" antigen. The factors concerned whether it be infection, drug, etc., may alter the original protein to the extent that it becomes antigenic. This mechanism may underly the production of some of the drug induced blood dyscrasias, the rheumatoid factor which behaves like auto-antibody to gamma globulin([7]), and the autoantibodies against DNA and RNA[8,9] which occur in lupus

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erythematosus. It is assumed that the body shows tolerance to the original proteins which occur in high concentration but shows little tolerance to the altered proteins as gamma globulin and compliment modified by combination of antigen and body complexes or the modified DNA and RNA, because of their low concentration in foetal and adult life.

(3) Autoantibody production may also follow immunization with bacteria, since some bactria contain antigens similar to or identical with human antigens. The blood group substances and Wassermann's antigen of bacteria are classic examples[10]. Others are the antigens related to heart and kidney in the streptococcus and those related to bowel antigens in Eschirichia coli and other Gram negative organisms.[11,12] In other cases, it is possible that the microorganism acts by altering tissue components or by liberating host components which are normally secluded. Perhaps evolutionary pressure has caused the microorganisms to develop surface componets which are similar enough to those of their host to limit the effectiveness of the host defences, although may be sufficiently different to cause autoantibody.

With regard to the second category in which auto-immunity is due to a disordered immulogical system, autoantibody production may follow:

(1) An inherited abnormality of the immune response to what are normally weak autoantigens. This inherited abnormality has been referred to by Burnet[2] as the "forbidden clones". As stated before, normally any group of clone of cells which possesses immunological reactivity for "self" antigens is rendered non functional either by some type of genetic repression or inhibition or by actual destruction. This elimination of potentially dangerous self reactive clones of cells is part of the process of immunological homeostasis. This homeostasis is presumed to be based on the destruction or inhibition of self reactive cells by contact with antigen, perhaps in some special environment such as the thymus, and perhaps at some particularly susceptible stage in differentiation of the cell line concerned.[14] Lymphoid cells undergo occasional somatic mutation or some equivalent change, thus becoming insusceptible to the homeostatic process. This would allow self-reactive or forbidden immunologically competent lymphoid cells to proliferate and initiate an auto-immune reaction[3]. Genetic factors are important in auto-immune disease, and may operate through the postulated homeostatic control over emergance of forbidden clones[4],

Failure of the homeostatic process or emergence of forbidden clones is assumed to occur in systemic lupus erythematosus. In the latter, forbidden clones are potentially reactive against a wide variety of autoantigens including different nuclear and cytoplasmic constituents, mitochondria, microsomes, and cardiolipin antigen associated with Wassermann type reaction[1].

(2) An acquired alteration in the immune apparatus whereby antibodies entirely unrelated to antigenic stimulation and directed against normal tissue, are produced. This is apparantly the case in certain malignant diseases involving lymphoid tissue as lymphomas in which autoantibodies against erythrocytes are produced and may be responsible for the development of haemolytic anaemia.

The Role of thymus gland in auto-immune disease. The clinical studies direct attention to the thymus in relation to various immune processes, including immunological homeostasis and development of forbidden clones[15]. Of particular relevance is the finding of various proliferative lesions and germinal centers in the thymus in both human and experimental autoimmune disease. These appearances could either reflect the origin of forbidden clones within the thymus or reflect changes in the thymus consequent to its being a site of immunological damage[13].

The relationship of auto-immunity to cutaneous diseases :

Let us now discuss how autoantibodies directed against the multiple antigens that constitute the skin are produced.

Keratin and distal epidermal cells undergoing keratinization might be considered foreign to the immunological system by virtue of their remote location and relative avascularity. However, the possibility of the normal skin components becoming antigenic resulting in the production of circulating antibodies is difficult to adapt with the phenomenon of immunological paralysis. Felton (1949)[16] demonstrated that large repeated injections of polysaccharides into normal mice would inhibit antibody formation to these antigens, and that antibodies could not be stimulated a long time afterwards by injection of amounts capable of inducing antibodies in the normal animal. Large doses of proteins do not produce immunological paralysis in the normal animal capable of producing antibodies[17], but they do greatlyr etard the detectable presence of antibodies, presumably because the excess antigen must be removed before free antibody can be released. If the proteins of normal skin were antigenic, the vast amount of material would either prevent antibody formation or immediately mop up the antibody [18].

Thus it seems more logical that autoantibodies against the skin can be produced following :

(1) Alteration of the epidermal cells by chemicals, radiations, burns or simple medical trauma, or as a sequel to inflammation.

(2) Sensitization to dander products which are of unknown specificity and usually associated with reagin type of antibody[18].

(3) Sensitization to microorganisms and their products contaminating the skin. Obviously, this is not autosensitization unless sensitization to skin tissue coexists[18].

(4) Furthermore, it is possible that the cutaneous antigens might be the target of spontaneously developing antibodies in diseases of abnormal antibody production by a disordered immune system[19]. Exfoliative dermatitis seen in association with malignant lymphoma is the skin analoge of the autoimmune haemolytic anaemia associated with that disease,

(5) Finally the skin may be the "battleground" of an entirely unrelated antigen antibody system and suffers the pathological alterations attendant upon such an event[20].

Cutaneous disease considered to be of autoimmune pathogenesis :

It should be emphasized that the demonstration of autoantibody does not necessarily indicate that the associated clinical state is of an auto-immune pathogenesis. Autoantibodies demonstrated in a disease may be a consequence of that disease and not the cause of it. This is the case in myocardial infarction in which autoantibodies directed against cardiac tissue may be produced. Also in viral pneumonia autohaemagglutinin may arise as an incidental consequence of the pathogenic agent. In these conditions, the autoantibodies has little to do with the clinical symptoms[21]. To implicate autoantibodies in the pathogenesis of any particular disease certain postulates, known as Witebsky's postulates[22], should be fulfilled:

(1) The direct demonstration of free circulating antibodies that are active at body temperature or of cell-bound antibodies by indirect means.

(2) The production of the specific antigen against which this antibody is directed.

(3) The production of antibodies against the same antigen in experimental animals.

(4) The appearance of pathological changes in the corresponding tissues of an actively sensitized experimental animal that are basically similar to those in the human or animal disease under study.

Although these postulates have come close to fulfilments in certain cases of human chronic thyroiditis (Hashemato's disease)[22], only few of these criteria have been met in most of the systemic diseases considered to have an autoimmunological pathogenesis[20]. Other characteristics of autoimmunity that serve as a guide to the detection of autoimmune disorders are the ,responsiveness of the disease to immunosuppressive agents including corticosteroids and cytotoxic drugs as 6-mercaptopurine and coexistence of the disease with other lesions attributable to auto-immunity.

In the field of cutaneous diseases there are few if any conditions of undisputed auto-immune pathogenesis. However, auto-immunity is implicated in some skin diseases on the basis of some tentative experimental studies or clinical characteristics.

I. Autosensitization Dermatitis :

The concept of autosensitization to skin was first introduced by Whitfield in 1921[23]. He described three distinct conditions in which autosensitization to skin may have taken place. In the first, extravasation of the patient's blood beneath the intact surface of the skin following local trauma resulted in generalized erythematous urticarial eruption 10 days later. He belived the eruption to be due to absorption of the broken down products at the site of injury to which the patient became sensitized. The second condition described by Whitfield was the exacerbation of persistent eczematous dermatitis of the leg (stasis eczema) followed 11 days later by a generalized heamorrhagic papular eruption. In Whitfield's description, this is the model which concerns those interested in the cause of idiopathic generalized eczema and to investigate its nature. The third form of autosensitization dermatitis described by Whitfield was the fluid liberated from vesico-bullous eczema lesions giving rise to

urticarial wheals and vesicles on the skin in the vicinity of the lesions, whereas the same fluid failed to give a re-action on Whitfield's own arm.

Unfortunately, this clinical concept has been given little experimental support. Although a precipitating event is important in autosensitization dermatitis and although tne disease can be suppressed with corticosteroid therapy, most of the postulates of Whitebsky have not been fulfilled. The antigen involved in this wide spread reaction might be bacteria that had infected the original site of dermatitis. However, recently Parish and Rook[24] demonstrated the presence of circulating antibodies against epidermal cells in two of 74 patients with autosensitization dermatitis. Although the presence of these antibodies favours the concept of antisensitization dermatitis, the limited number of positive patients in this study suggests that the antibodies demonstrated by Parish may be the incidental byproduct of wide spread dermatitis. This would indicate that an immunological mechanism need not be postulated to explain the pathogenesis of this disease.

II. ***Exfoliative Dermatitis :***

It seems possible that the generalized exfoliative dermatitis that develops in association with lymphomatus disease arises because of autoantibodies to skin produced by primitive disordered lymphoid cells in a manner analogous to the autoimmune haemolytic anaemia associated with malignant lymphoma.

III. ***Purpuric Eruptions :***

Autoantibodies are rarely formed against constituents of tissue in close contact with the lymphatic apparatus. Consequently auto-immune reactions involving the vascular system or elements of the blood would only occur either from :

(1) Significant alterations of these tissues making them autoantigenic.

(2) Production of abnormal antibodies by a defective immunological system, reacting with normal tissue.

In systemic lupus erythematosus, thrombocytopenic purpura is caused by auto-antibodies against platelets[25]. Hypersensitivity to desoxyribonucleic acid (DNA) was associated with spontaneous painful haemorrhagic nodules on the extremities[26,27]. In these conditions skin testing with very small quantities of DNA reproduced the clinical lesions.

Other cutaneous diseases that deserve investigation for similar auto-immune phenomenon are the chronic pigmented purpuric eruptions, Henoch-Schoenlein purpura and the many categories of dermal vasculitis of undetermined cause[20].

IV. ***Erythema gyratum and erythema multiforme :***

Shelley and Hurley[19] described the association of erythema gyratum, massive breast hypertrophy and generalized pigmentation. They were able to demonstrate in the patient's serum an autoantibody directed against the cystic breast tissue. The authors were of the opinion that the breast antigen was fixed in the skin. The erythema represented autoantibody reaction in the skin denoting that the skin was the

"battle ground" of an entirely unrelated autoantibody antigen system, suffering the pathological alteration attendant upon such an event.

Ludlam et al (1964)[22] found a high titre of antibody to Mycoplasma pneumoniae, the cause of primary atypical pneumonia, in patients with erythema multiforme. This raises the question whether immune or auto–immune processes may be important.

Pyoderma Gangronosum :

Pyoderma gangrenosum usually occurs in association with various debelitating systemic diseases particularly ulcerative colitis, since patients with ulcerative colitis have been found to have circulating autoantibodies directed against the mucosa of the colon. The destructive, ulcerative lesions of pyoderma gangrenosum may result from autoantibody antigen reaction in the skin between these antibodies and common antigenic factors in the skin.

Long and Uesu (1964)[29] reported two cases of pyoderma gangrenosum associated with ulcerative colitis in which autologous skin grafts were rejected and delayed reactions to the intradermal injection of autologous leucocytes occurred.

Systemic lupus Erythematosus :

This is a disease in which familial and probably hereditary factors are important and in which there is multiple autoantibody formation, including the production of antibodies to nuclei, cellular cytoplasmic components, red blood cells, platelets and some evidence of delayed hypersensitivity to autologous components [4,13]. Patient with this disease are unduly prone to drug reactions and gives enhanced immune responses to test antigens and there is evidence that relapses of the disease may be triggered off by exposure to foreign antigens [4,13]. The underlying nature of the disease is not clear. It is customary to speak of an impairment of immunological tolerance, or of the occurrance of clones of cells able to produce autoantibodies which arise through somatic mutation, and a reduced ability of the homeostatic mechanism to control them[4].

Discoid Lupus Erythematosus :

The current clinical impression that discoid lupus erythematosus is a benign cutaneous variant and infrequent precursor of systemic lupus erythematosus seems to have gained immunological evidence. Antinuclear antibodies have been demonstrated in more than 50 per cent of patients with discoid lupus erythematosus [30,31]. These antibodies are reactive against epidermal cell nuclei as well as the nuclear material of the heterologous leucocytes.

However, we are still confronted with the question : are these antibodies the primary incitants of this complex disease ?

Scleroderma : (System Sclerosis) :

Antibodies against nuclei were found in 25 out of 32 cases of scleroderma. The incidence of antibodies against nucleoli was much higher than in systemic lupus

erythematosus [32]. The finding of antinuclear antibody in patients with widespread cutaneous scleroderma and morphoea suggests that these diseases may stand in the same relationship to systemic sclerosis as chronic discoid lupus does to systemic lupus erythematosus [13].

Dermatomyositis :

Dermatomyositis in adults shows a stricking association with internal malignancy [33]. This fact has urged the study of patients with dermatomyositis and visceral carcinoma for an immunological relationship between the tumour and the skin and muscle disease. Antibodies against nuclei were found in a few patients. Antibodies against muscle have not been reported [13]. In general, muscle leslons are associated with cellular infiltrate, and in some patients the subject shows immediate type hypersensitivity to his own tumour and which can be transferred by serum [34].

It is not known whether there is an immune response against muscle or against a factor which adheres to the surface of the muscle [13].

Bullous Diseases :

Generally bullous diseases are chronic illnesses which respond to corticosteroid therapy and in some instances are evidently allergic, e. g. drug induced bullous erythema multiforme. So it seems likely that this group of diseases would include examples of true auto-immune cutaneous diseases. Investigations have been carried on pemphigus vulgaris, in particular, because of the specific nature of the pathological lesions which would suggest that autoantibodies directed against epidermal cells are implicated in this disease. Circulating antibodies against epidermal cells in the serum of patients with pemphigus vulgaris were demonstrated by Jordan et al [35]. However, such antibodies could not be demonstrated by others. Further investigations are required before any conclusion can be reached.

Atopic Dermatits :

Investigation of atopic eczema as a disease of autoimmunization to cutaneous antigen was undertaken by Hashem et al [36]. They found that lymphocytes obtained from infants with severe infantile eczema were induced to undergo mitosis when grown in a culture containing a cell-free skin extract. Hashem concluded that the lymphocytes of the eczematous infant were sensitized to a component of skin, that is to a homologous antigen. The cells thus sensitized respond by division and reversion to a more primitive from. However, the work of these authors needs confirmation and elaboration since the cutaneous extract was derived from biopsy specimens and a contaminant bacteria or fungi may be the sensitizing antigen.

Psoriasis and Psoriatic Arthritis :

The association of the psoriasis with rheumatoid arthritis, its chronicity, response to corticosteroids and its familial pattern suggest a similarity to auto-immune disease. Circulating antinuclear factors were demonstrated in two patients with psoriasis with

arthritis and in one patient with psoriasis without arthritis[20], but these findings have to be confirmed before implicating an auto-immune mechanism for that disease.

Vitiligo :

Lorincz and Rothman (1959)([37]) proposed the hypothesis that vitiligo may represent a low order auto-immune disease whereby antibodies directed against tyrosinase enzyme are produced. This concept was based on the association of vitiligo and Vogt Koyanagi and sympathetic ophthalmia, both of which can be interpreted as uveopigmentary sensitization syndromes. It is believed that in these conditons melanin granules are released from the melanocytes. The displaced melanin can act as an antigen provoking the production of tyrosinase antibodies. The depigmentation caused by chemicals toxic to the melanocytes as monobenzyl ether of hydroquinone can also be similarly explained. It is believed that a neurochemical factor, if any contributes to the development of vitiligo, may act by allowing the release of the antigen from the melanocyte or by making it more accessible.

However, disruption of the melanocytes with release of melanin occurs in many inflammatory and neoplastic conditions of the skin and which is not associated with vitiligo. Also vitiligo is not associated with any of the known auto immune diseases. Immunological studies seem to stand against auto-immune pathogenesis for vitiligo. Antibodies induced in rabbits against mouse melanoma, although they exhibited a moderate inhibition of tyrosinase in vitro they failed to do so in vivo.

Sjogren's Disease :

Like lupus erythematosus it is characterized by multiple autoantibody formation.[13] The disease is familial and there is an increased incidence of autoantibodies in relatives.[38] The occurrance of antinuclear factor and compliment fixing antibodies to cytoplasmic antigens and of the rheumatoid factor in the majority of cases is documented by Bunuim et al.[39]

The Relation between Neoplasms and Auto-immune Disease :

(1) *Tho auto-immune disease as a precursor of Malignancy*: Antibodies directed against a cell surface may cause cell division[40,41,42] which may be mediated through changes in the lysosomes. Green[43] suggested that immunological reaction against a group of cells might select a cell line lacking a critical component and that this lack might favour carcinogenesis. It might also be expected that tissues subjected to recurrent cycles of cell death and proliferation would be unduly prone to carcinomatous changes.[13] Clinically, there is an increased incidence of carcinoma of the affected organs in pernicious anaemia and ulcerative colitis. Bronchiolar carcinoma is a rare complication of pulmonary fibrosis due to scleroderma.[44]

(2) *Malignancy as a precursor of auto-immune disease :* There are several examples of the occurance of autoantibodies in neoplastic disease of the lymphoid system. Antibodies against erythrocytes had been found in one fifth of patients with chronic lymphatic leukaemia, lymphosarcoma and Hodgkin's disease.[45] Also there

are several curious complications of circinoma which are not due to local metastasis and which resemble auto-immune disease, These include dermatomyositis,[46,47] carcinomatous myasthenia graves,[48] annular erythema[49] and range of neurological disorders including cerebellar atrophy, wide loss of cortical neurons and peripheral neuritis.[50]

There are several possibilities for the origin of these autoantibodies.[13]

(a) They may be secreted by neoplastic cells. Some tissues secrete products which are not produced by the parent cell line.

(b) It may be that certain tumours produce materials which are similar but not identical to normal body componences and thus cause an auto-immune response.

(c) Alternatively the tumour cells may sectrete an antigen which attaches itself to other cells.

(d) The autoantibodies may be produced by normal cells in response to the agent which caused the neoplastic process.

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