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## Auto-immunity Fact or Fiction

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### Abstract

Read before the Society Wednesday 14th January 1970.

The recognition that the mammalian organism is capable of developing an immune response against its own normal tissue components has aroused interest in the implication of auto-immune reactions in human disease. This interest may, however, be too widely applied, and the label "auto-immune" may be applied to a particular clinical entity with a complete disregard for the rather exacting criteria which this aetiology demands; indeed one might say that the word auto-immune is almost synonymous with the word idiopathic, in the clinician's dictionary.

Some definitions first. By auto-immune disease it is widely understood that there is a failure at some point for the body to differentiate between its own tissue components and those of a foreign material; it can no longer distinguish, if one likes to put it in more crude terms, between "self" and "non-self". Consequently the host launches an immunological response towards its tissue components, with the resulting pathological changes and clinical manifestations.

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# **AUTO-IMMUNITY**

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The recognition that the mammalian organism is capable of developing an immune response against its own normal tissue components has aroused interest in the implication of auto-immune reactions in human disease. This interest may, however, be too widely applied, and the label "auto-immune" may be applied to a particular clinical entity with a complete disregard for the rather exacting criteria which this aetiology demands; indeed one might say that the word auto-immune is almost synonymous with the word idiopathic, in the clinician's dictionary.

Some definitions first. By auto-immune disease it is widely understood that there is a failure at some point for the body to differentiate between its own tissue components and those of a foreign material; it can no longer distinguish, if one likes to put it in more crude terms, between "self" and "non-self". Consequently the host launches an immunological response towards its tissue components, with the resulting pathological changes and clinical manifestations.

The subject of auto-immunity has however, like so many other intensely investigated fields been clouded by vague and indeed, often confusing, terminology. The term auto-immunity at present enjoys the widest use, and under this rather nebulous heading are included many diseases resulting from the reactivity of antibodies directed toward the host tissues. These diseases range from Hashimoto's thyroiditis, and rare forms of haemolytic anaemia right through to disseminated lupus erythematosus, rheumatic fever and dermatomyositis.

Before we even begin to consider exactly

what significance the immunological response has in these diseases, we can perhaps make a few pertinent points.

First, it can be shown, and this will be discussed in more detail later, that the auto-immune process plays an intricate, and perhaps as yet incompletely revealed part in the process of cellular damage. It still remains to explain how the process came to be in existence; so that, when we use the term auto-immunity we are describing a particular pathogenic mechanism; we are not forwarding an aetiology. Auto-immunity is a process, like degeneration is a process; it does not explain how this process came about.

Second, auto-antibodies, and, presumably, auto-reactive delayed hypersensitivity, can occur as a result of tissue damage. Trauma to an organ may lead to cellular necrosis and death, with the liberation of tissue components, and these tissue components may elicit an immune response; but this need not be an aggressive response. One example is that of the post myocardial infarction, or Dressler, syndrome. Following myocardial infarction, antiheart antibodies, as detected by both indirect immunofluorescence and antibody consumption tests were present in the serum of recovering patients, but absent from that of controls. Following recovery, the levels of these antiheart antibodies fell to undetectable levels. Dressler suggested that cardiac necrosis may lead to this auto-immune response. In rabbits certainly, animals immunised against rabbit heart do not develop any histological changes in the myocardium, despite high levels of circulating antibody. Kaplan found transient antiheart antibodies were sometimes

present after heart operations, especially commissurotomy. Antibodies to liver are found in rats following administration of hepatotoxic agents. Therefore the demonstration of an auto-immune response, i.e. the detection of antibodies towards the host's own tissues, does not seem, in itself, to provide good evidence that tissue damage in disease has an immunological cause.

Unfortunately this concept is not so well instilled into many of our minds as it could be. Auto-immunity is not synonymous with auto-aggression. And yet, the immune mechanism need not invariably benefit the host — the anaphylactic response, with its often fatal outcome, is a dramatic example to the erring physician.

It may be seen that an auto-immune process can play a part in the perpetuation of a pathological situation. A question that must be answered is that if, once initiated, the process is self-perpetuating, or whether the original perturbation is necessary for the continuation of the pathological state. In other words how important is the immune process in the prolongation of the disease. This problem can be tackled from several angles.

One must be immediately put on one's guard by the observation that many auto-immune antibodies can be present without overt pathological damage. The Wasserman reaction, for example, demonstrates antibody to cardiolipid — a phospholipid which occurs in mitochondria of mammalian cells. This auto-antibody develops after several types of virus infection, including vaccination and glandular fever; diseases in which there may be minimal observed tissue damage. It is perhaps worthwhile first to consider that perhaps if the spirochaete had not been observed and isolated in cases of syphilis, this disease too, in the light of a positive antibody reaction to heart tissue, may have been found in the ranks of the auto-immune disorders.

One method of determining the relationship of the genesis of the sensitised state to the prolongation of the clinical disease is to see if damage to the corresponding organ follows injection of extracts of various tissues, and if, once initiated in this way, the process is self-perpetuating. Field and Laspari attempted this with testis and brain and found that the lesions produced in the target organs tended to decrease in intensity once the course of infection was terminated. However, the organ that has received the greatest amount of

attention concerning this aspect of research has undoubtedly been the thyroid gland. It was early discovered that the serum of patients with Hashimoto's thyroiditis contain auto-antibodies against thyroglobulin, that this antibody is organ specific and that it does not cross react with extracts of thyroid glands from the six other mammalian species studied. Since then, antibodies toward microsomal thyroid antigen have been discovered. Experimental immunization of animals with homologous or autologous thyroid extracts should, and indeed does, lead to the production of circulating thyroid antibodies and to lesions within the gland virtually indistinguishable from the pathological appearance of Hashimoto's disease. There is, however, no consistent relationship between the level of circulating antibodies and the severity of thyroid lesions, at least in neither rats nor rabbits. However, the injected extract has an important bearing on the results — aqueous preparations of thyroglobulin are rapidly catabolised and do not persist as a sustained stimulus. In the case of injections of thyroglobulin incorporated with complete Freund's adjuvant the stimulus is sustained. Homologous thyroid extracts without adjuvant do not produce a rise in antibodies or a thyroiditis, it is only when thyroglobulin plus adjuvant, or thyroglobulin that has been altered chemically by coupling onto a diazonium derivative is used that any measurable response is obtained. Once the hypersensitive state is attained, using altered thyroglobulin, subsequent injections of unaltered thyroglobulin do not perpetuate the response indefinitely. An interesting result since recent work has demonstrated that thyroglobulin is physiologically secreted into the lymphatics.

We saw that in the case of Hashimoto's thyroiditis which has been experimentally induced, the level of antibodies does not correlate well with the degree of pathological damage within the gland, and so we need to consider the relative importance of delayed hypersensitivity and antibody, or humoral factors in auto-immune disease. In certain cases, for example the haemolytic anaemias, the antibody is almost certainly more important. In the experimental field a transient allergic glomerulonephritis can be induced by the transfer of large amounts of serum from an auto-immunized host developing antibodies towards its own kidney.

In other auto-immune disorders however,

delayed hypersensitivity may be important. Evidence that both delayed hypersensitivity and antibody production was important in the pathological response was forwarded by Brown et al, working on experimental orchitis in guinea pigs. They defined a system, using differently prepared tissue extracts, whereby in some animals only antibody toward the testes developed, and others in which only a delayed hypersensitivity phenomenon developed. In neither case was there a characteristic orchitis. Only when antibody was transferred to animals of the delayed hypersensitivity type, or cells transferred to the animals in whom antibodies had developed was the characteristic testicular damage obtained. So in this experimental situation both and cell mediated factors may be important.

Whilst we know that auto-antibodies may be present in a large number of diseases, what do we know of the aetiology of these so called auto-immune diseases. There may be several ways in which the auto-immune process may be initiated and the aetiological factor might have to be present for the auto-immune process to be continued. One needs to consider the several types of auto-immune disorder.

First, there is the group of diseases in which the auto-immune disease follows infection; and the obvious syndrome illustrating this is rheumatic fever, following a streptococcal infection of the throat. Kaplan has shown that auto-antibodies to heart occur in acute rheumatic fever and that some, but not all, of these react with streptococci. Rabbits immunized with streptococci develop auto-antibodies, and antibodies toward human heart. It may be that the antigens of streptococci and heart tissue are similar or it may be that streptococcal antigens react as haptens.

Let us now consider some auto-immune diseases such as thyroiditis. Current thinking about aetiology of this condition must surely change, for although the label auto-immune is applied, it is, as I have endeavoured to explain, merely describing the process, not the aetiology. Current thought revolves around the discovery that often a family history is obtained in these patients, and that many people who are clinically normal have high levels of thyroid antibodies, within these family groups. Indeed Hall and Stanbury having recently examined a number of families affected by the condition have shown that the incidence approached 50% in siblings and that there is almost invariably an abnormality in

one or other parent of an affected patient. This is compatible with dominant inheritance, and in the families they examined figures approaching theoretical were obtained. In other families, both other genetic factors and indeed environmental pressures such as iodine deficiency, puberty, pregnancy and viral infections, may need to be suitable before the disease manifests itself.

Experiments in the New Zealand Black Mouse strain and its hybrids are also of interest here. Mice of this strain appear normal at birth, but between four and nine months of age develop a haemolytic anaemia analogous to human auto-immune haemolytic anaemia. The first abnormality detectable is that their circulating red cells begin to give positive direct antiglobulin tests and eventually the test becomes positive in virtually 100% of the mice. The results of crossing of this type with other strains show that the auto-immune character of NZB mice is expressed in different ways, but is present in its  $F_1$  hybrids. It is not influenced by the sex of the NZB parent and this indicates the transmission of disease to the offspring is not sex linked, and the milk factor does not seem to be involved.

How might — and I assume for the process of hypothesis — this genetic abnormality of the thyroid manifest itself in physical terms?

It could of course be a lesion leading to faulty protein structure within the thyroid follicular cell. This might lead to abnormal release of normal constituents and this continuing cellular damage might elicit the "auto-immune" response. If this is so, one might wonder why the clinical presentation is so late in life. Environmental reasons have already been proffered but it is worthwhile remembering that diseases such as Huntingdon's chorea, widely recognised by clinicians as an autosomal dominant inherited disorder, does not normally present until the middle thirties in those affected and it may be even later.

This is an attractive hypothesis, for it may also lead to an understanding of the association of auto-immune thyroiditis and of Addisonian pernicious anaemia, the latter being a disease in which over 80% of patients have antibodies to gastric parietal cells. The thyroid and the gastric mucosa have a common embryological precursor — namely the endoderm — and furthermore several similar biochemical functions — for example, the ability to concentrate iodine. It might be considered that if a biochemical defect existed in the

thyroid cell, and there are a vast number of possible defects, some of them might not only affect thyroid biochemistry, but gastric metabolism as well, the two cells sharing common pathways.

Another defect might be that instead of the thyroid being abnormal there is defective control in antibody production. I find this less satisfying; why is the "control" always lost to certain specified organs — thyroid, gastric mucosa, adrenal glands. On the tissue defect hypothesis it might be said that if the defect were in a more vital tissue — muscle, liver — this would be incompatible with life and the conception would never go to term.

The aetiology of auto-immune diseases may also be infection. Subacute sclerosing panencephalitis is a degenerative disorder of the brain, the exact aetiology obscure. Antibodies to brain were discovered in these patients and the label auto-immune attached to the syndrome. It is only recently that antibodies to measles virus have been isolated in these patients, and it may be that the virus is slowly

causing brain cell damage and subsequent immune response. This syndrome may be elevated from auto-immune status to delayed infection status, a much more clearly comprehended pathology.

And so, the course is clear. Research must now be directed towards distinguishing auto-immunity as an epiphenomenon after tissue injury, from that which is more intimately concerned with the pathogenesis of specific disease. That the body can produce antibodies to its own cells is fact, but this does not imply disease, indeed the increase of lymphosarcoma in patients with intensive immunosuppressive therapy, and the increase in incidence of bowel tumours in patients with multiple myeloma might suggest that immune processes play an important part in the clearing of cellular debris and the prevention of abnormal or neoplastic cells arising. A full answer must await the elucidation of the control of the immune response, its magnitude and direction, and a fuller understanding of what is so vaguely termed immunological response.

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