Autoimmunity

The Lewis-Cameron Undergraduate Prize in Bacteriology, 1963.
"To cure when possible, to relieve when necessary, and to comfort always"—this has ever been the aim of the physician. Despite the many advances in medicine over the last half-century, there are still too many diseases in which, through our ignorance, only the last principle can be achieved.

Medicine is unique among the sciences in that the quest for knowledge is not pursued primarily for intellectual satisfaction, but for the hope of bringing relief to the diseased and the helpless. The methods employed in the attainment of this end are not those of the detached and scientific mind; of propositions, experimentation and verification. From the start, the medical scientist is confronted by complexity, and, for clues provided by investigation, the final solution is found in a retrograde manner.

In the manifest impossibility of starting from simple principles and the inherent weakness in medical investigation, and, in addition to this, there are few rules which can be used to guide the inquiring mind. Hence it is inevitable that mistakes shall arise, and the problem become obscured, until confusion, before the parameters are resolved and a clear solution to the problem is found.

Bearing in mind the present inadequacy of my evidence, I have not attempted to reach, in this essay, any concrete conclusion, but rather I have devoted it to a very general survey of the subject with a few comments and insights upon interesting points.

The subject of auto-immune disease is one, with many other conditions, vast scope and terrifying complexity. It is, then, a subject to be treated with respect and humility, and will prove challenging for the gallant attempts made to master the ignorance, by experimentation and study, which has concerned us for so many years.

Before discussing these defiles to which the immunological processes are subject, it is necessary to survey the mechanisms involved. The main functions of which these processes are believed to be implicated may be divided into inherently beneficial and potentially detrimental effects. Between these two there exists a "balance of power," which, if disturbed, results in the detrimental effects, predominating and the beginning of disease.

Detrimental

Beneficial

Local tissue reactions
Systemic hypersensitivity reactions
"Auto-immune" disease

Defence against invaders
Endo-physiological organization
"Integrity" function
The cell is the basis of all immunological phenomena. All the cells in the body participate, to some extent, in immunological processes, but the true of initiating and regulating these responses lie with the cells of the reticulo-endothelial system, hereafter referred to as the RES. This is a loose term describing an association of two main types of cell, the fixed and wandering macrophage, and the cells concerned with antibody production and dissolution. Almost certainly these two groups stem from one type of cell, the primitive reticulum cell found in lymph node, thymus, spleen and bone marrow.

An associate of the reticulo-endothelial cells, implicated in certain phenomena consequent to local tissue sensitivity reactions, the mast cell or histocytic basophil, must be mentioned. It is found in close association with blood vessels in superficial tissue, and is responsible, by means of the histamine, protease-peptides, and serotonin it releases, for the vascular phenomena seen in such reactions.

The macrophages produced by the reticulum cell are of two types, a large cell fixed to the reticular framework of the parent organ, and a smaller wandering phagocytic cell, the free macrophage. These have been termed the “scavenging cells of the body” from their ability to ingest dead tissue and bacteria.

Lymphocytes are formed from “primithe reticulum cells in the lymph nodes, thymus, and spleen. They may be seen in association with these fixed macrophages engaged in phagocytosis. The lymphocytes are present in great numbers in both blood and lymph, and exhibit a circulation from lymph node to the blood, and back to the lymph node again remaining in the circulation for about 2 hours. The life span of lymphocyte from thymus to lymph varies from a few hours to one hundred days. Two types of lymphocyte, termed “large” and “small” are recognised, and present evidence indicates that both are capable of division under special circumstances. The lymphocyte is capable of mild phagocytosis, not a pinocytosis, and ameboid movement. Reticular to these cells is their ability to enter and leave other cells of the body at will.

In addition to lymphocytes the RES produces plasma cells. These are formed in the lymph nodes and thymus and bone marrow after suitable antigenic stimulation. Their cytoplasm, rich in ribonucleic acid, is ideally suited to the formation of protein antibodies and this seems to be their function. How the correct specific antibody is formed is at present a matter for conjecture, but will be considered upon later.

Allied to, but not synonymous with the RES cells, are the granular blood forming cells, and the white corpuscles.
It has been shown that in irradiated mice, cells of the lymphoid series can give rise to bone marrow cells, and vice versa. This interchangeability of cell type is perhaps not surprising when considering their common embryological origin.

The functions of each cell type are incompletely known. The phagocytic cell of the reticulum is it free or fixed is capable of ingesting particulate antigenic matter. This is then "passed on" to the plasma cell in a modified form to excite the production of antibody. This passage is perhaps analogous to the passage of iron from the haemocyte to the mononuclear in the bone marrow, or may be the function of an intermediate lymphocyte. The plasma cell then elaborates the corresponding antibody by a mechanism involving "messenger RNA" and the ribosomes, possibly similar to the process of gene replication in dividing cells.

Burnet believes that antibody forming potentiality is a genetically determined quality of certain clones of mesenchymal cells. The presence of antigen stimulates one or more of these clones to proliferation and antibody production, after passing through a transient phase in which they are susceptible to destruction or inhibition on further contact with the antigenic stimulus. This theory depends upon there being a high degree of genetic mutability at some point during antigenic stimulation, or at some time during embryonic life; enough, in fact, to provide a range of clones capable of reacting with all foreign antigen patterns.

The essential difference between Burnet's theory and the "classical" theory of antibody production is that in the former, a kind of Darwinian selection of useful cells is assumed to occur in embryonic and later in adult life, while the latter antibody is essentially Lamarckian concept of the mesenchymal cell being able to modify its antibody producing pattern on gene in the presence of a suitable antigen. It is now believed that the second process is the one which occurs in a single organism, like paramyxovirus, observations have shown the ability of the single cell to vary its constitution to suit environmental conditions.

In either case, this should be, unless our premises are false, some mechanism by which the R.E.S. "recognizes" the cells which surround it as "self" and does not destroy, harbouring to them. It has been suggested that this first takes place in the thymus, and from here subsequent colonization of the body's lymphatic tissue takes place. The thymus gland is capable of considerable lymphoid mass expansion during antigenic stimulation, with formation of thymic glandular areas, lymphoid follicles and plasma cells. Most cells and recognizable areas appear, giving the typical appearance seen in the thymus during the course of regenerative and immune responses.
Lymph nodes, draining the antigenically stimulated area, become red in plasma cells, and produce a polynucleotide substance which will increase the reticular cells in lymph nodes and spleen. A reduced proliferation rate, with a drastic reduction in the production and maturation of lymphocytes and plasma cells in the thymus and lymph nodes. Hodgkin’s lymphadenoma often produces a similar histopathological picture of reticular hyperplasia and lymphocytes.

The antibodies produced by the plasma cells are found in the Ig globulin fraction of the plasma proteins. They are glycoproteins of a molecular weight 150-180,000 and an isoelectric point at pH 6.7-7.3 in the range of body pH because they possess an electron balance and are therefore not susceptible to special distortion by imbalanced electron charges. The shape of the molecule determines its antigenicity and this it keeps very well in spite of rough chemical treatment. Up to 34% of the molecular weight may be lost without spoiling the specific special relationship. Most of the Ig globulin fraction consists of immunologically inert protein, the origin of which is not known. It may be simply the raw material waiting to be converted into immunologically active protein by the plasma cell, or antibody formed to “non-antigens,” such as the polysaccharides of some plants, or to certain antigens with crystalline patterns which could stimulate antibody formation, like melitta or asbestos.

The function of antibody is to coat the foreign antigen, rendering it chemically inert, to provide a “sticky” surface facilitating phagocytosis (opsonization) and to induce lysis of the complex with eventual enzymic destruction. In the lysis it is aided by two systems of enzyme-like proteins, complement and properdin. Complement has four or more components which are heat-labile. In the presence of specific antibody, the complement system will cause lysis of the offending antigenic particle, becoming itself “fixed” and rendered thereafter inert in the process.

Properdin is a globular protein with a molecular weight of about 9 x 10^6. It acts with some component or components of the complement system to cause lysis. Magnesium ion is necessary for the activation of this system.

The complement/properdin systems have been termed part of the “non-specific defense mechanism of the body, but so little is known about them it would be dangerous to suppose they have no other function.”

The functions of the reticuloendothelial system in disease caused by microbial invasion are essentially to limit the
spread of the organism, and to destroy it. Several kinds of response
are seen in "infectious" diseases, a straightforward immune response,
and a rising tide of antibody to the organism or its products,
local tissue responses at the site of invasion, and a hypersensitivity
reaction, sometimes called the delayed response, which may be allergic
in character. The last response is a feature of the main granulomatous
conditions, syphilis, tuberculosis, leprosy, and the myotic infections, and
is present in the "autoimmune" diseases. The one must remark upon
the similarity, both immunologically and clinically, of the infectant
granuloma to autoimmune disease. The significance of different
infective agents provoking very similar disorders, both in duration,
and in the response of the body to the infection, leads one to
believe that the disease produced is not due to the direct toxic
or invasive attributes of the pathogen, but lies in the body's reaction
to them, a direct bacterial challenge to the body is met with
a type of reaction in which the organism and the body's own
cells themselves are destroyed indiscriminately. Diagnostically the
autoimmune diseases resemble these granulomas; at one time
it was thought that diabetic lipoid nephritis was a cutaneous
sedimented infection. Moreover, the ability of dead mycobacteria,
used as an adjuvant in experimental induction of autoimmune
disease, to cause sensitization to the infected tissue antigens, is
probably a reflection of their curious effects when causing disease
in the normal state.

The other function of the immune response exceeds the simple
defense of the individual. Entepoliticians have sieged upon the
antigen-antibody response to provide a model for the explanation
of immuneological organization. Weiss is of the view that this phenomenon
depends upon the "stickiness" of the cell surface which allows it
to adhere only to cells of its own kind or to its developmental neighbour.
The further asserts that "antigen-antibody" control of the surface
antigens, and hence the adhesion of the cells, accounts partly for
the body's ability to maintain and repair its own structure.
It is well known that tumour cells often lose this adhesive
property, and that antibody-coated red cells are "stickier" than
the normal cell. It has been suggested that leukaemia is essentially
a failure to prevent abnormal cells of the marrow proliferating, and
that autoimmune disease may be caused by a failure of the
body to eliminate harmful cell clones of the lymphoid series.
From this point of view one could almost regard tumour formation
and autoimmune disease as being due to a failure in one
or other aspect, of the body's ability to regulate correctly its own
structure (4, 39, 41)
The value of the immune response in destroying microbial invaders is easily understood, yet it has been proposed that some diseases may be caused by disturbances of this system of defence, resulting in the formation of antibodies to tissue cells and their eventual demise. The precise lines of enquiry seek to establish whether or not this is the case; does a perturbed RBC attack the tissues of the own body, or are the immunological features of autoimmune disease merely a reflection of some unknown and hitherto unsuspected disorder? Whatever the ultimate outcome of this enquiry, the immunological study of these previously incomprehensible diseases has established a similarity, at least superficially, between them.

Before being able to assign a disease process to the class of autoimmune diseases, it is agreed that certain criteria should be satisfied. These are below: 

1) Demonstration of free circulating antibody active at body temperature, or the demonstration of cell bound antibody by direct means.
2) Recognition of the specific antigen against which the antibody is directed.
3) Production experimentally of antibodies against the same antigen in experimental animals.
4) Appearance of pathological changes in the corresponding tissue of an actively sensitised animal that are similar or identical to those seen in human disease.

At present these criteria are a little too rigorous for explicitation in every case of autoimmune disease, certainly those in which the specific antigen or antibodies are not known. These diseases at present suspected or "proven" to be of autoimmune aetiology are shown in the table opposite.

It can be seen from this table that the autoimmune diseases form a spectrum from extremely specific diseases involving one tissue and perhaps even one antigen, represented by the presence of highly specific antibody, to those in which a wide range of non-specific antibodies (immune complexes) or antibodies to low specificity are encountered.

The presence of antibody to a tissue may theoretically damage that tissue in a number of ways. Here are briefly, an Arthus type of reaction, resulting in vascular damage to the organ concerned, a delayed hypersensitivity reaction, a direct cytotoxic action, and disseminated vascular damage by intravascular coagulation by red cell antibodies, and the indirect cytotoxic action.

There is evidence that an Arthus type of reaction may lead to homograft rejection (although this is scarcely an autoimmune disease) and it may also be responsible for the renal lesions seen in glomerulonephritis.

The indirect cytotoxic action due to the coating of the cell
<table>
<thead>
<tr>
<th>Disease involvingQUIRED antigens</th>
<th>Disease</th>
<th>Nature of Antigen</th>
<th>Nature of Antibody</th>
<th>Influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto Disease</td>
<td>Thyroglobulin</td>
<td>Antibodies, ACF.</td>
<td>Neir Gruen et al.</td>
<td></td>
</tr>
<tr>
<td>Lupus</td>
<td>Unknown</td>
<td>Auto-antibodies, ACF.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Syphilitic Lupus</td>
<td>Lues antigen</td>
<td>Antibodies, ACF.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Potentially a foreign antigen</td>
<td>ACF, ANF (16 cells),</td>
<td>BR Senn, WR Boyd.</td>
<td></td>
</tr>
<tr>
<td>Lymphatic Lymphoma</td>
<td>Unknown</td>
<td>ANF.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>Minimum</td>
<td>ACF.</td>
<td>2.7 l.h.</td>
<td></td>
</tr>
</tbody>
</table>

| Disease associated with common antigen | | | |
|----------------------------------------| | | |
| Allergic Asthmati | IgE antibodies, globulin | ACF, ANF, Lues | J.B. Herod, M.M. Neir, |
| | | B.B. Herod, M.M. Neir. | 1.1 Felion et al. |
| Systemic Lupus | Nucleo-cytoplasmic components, Platelets | ACF, ANF (16 cells) | - |
| | factors, Leukocytes | Anti-nucleo-cellular | |
| | | | |
| | Platelet antigen | Anti-platelet, Anti-nucleo | |
| | | | |
| Pernicious Anemia | intrinsic factor | Auto-antibodies, ACF. | |
| | | | |
| Thyroiditis | Thyroglobulin | Antithyroid, ACF. | |
| Autoimmune | | | |
| Drug-induced | | | |
| Hypothyroidism | | | |
| Classical Hemolytic | | | |
| Immune | | | |
| Drug-induced | | | |
| Drug-induced | | | |
| Drug-induced | | | |

**Notes:**
- ACF: Autoimmune complement fixing factor.
- ANF: Anti-nuclear factor.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Nature of Antigen</th>
<th>Nature of Antibody</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever</td>
<td>Streptococcal product</td>
<td>Anti-Streptococcal</td>
<td>Kaplan &amp; Karpstein 1966.</td>
</tr>
<tr>
<td>Ehrlich's I</td>
<td>Streptococcal product</td>
<td>Anti-streptococcal</td>
<td>Boyd &amp; Karpstein.</td>
</tr>
<tr>
<td>Myocarditis, pericarditis, and meningoencephalitis</td>
<td>Unknown</td>
<td>Various</td>
<td>Kaplan &amp; Smith.</td>
</tr>
<tr>
<td>Exponentially produced</td>
<td>Glandular fraction of</td>
<td>Anti-glandular</td>
<td>Boyd.</td>
</tr>
<tr>
<td>Meningitis (Kaplan)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse Encephalitis</td>
<td>Brain + adjuvant</td>
<td>ANF, Anti-murin and anti-brain antibodies</td>
<td>Boyd.</td>
</tr>
<tr>
<td>Homologous disease</td>
<td>Cells of host animal</td>
<td>Various</td>
<td>Kaplan.</td>
</tr>
<tr>
<td>Mononuclear reaction</td>
<td>Grafted cells</td>
<td>ANF and others</td>
<td>Kaplan &amp; Smith.</td>
</tr>
<tr>
<td>Auto immune disease</td>
<td>Not yet proven</td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Myelin or precursor?</td>
<td>Anti-axonal cell?</td>
<td>Boyd &amp; Green.</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>With protein, mucosal factor?</td>
<td>Anti-lactealsin</td>
<td>Taylor &amp; Thiele.</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Connective tissue</td>
<td>Unknown</td>
<td>Boyd.</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Connective tissue</td>
<td>Unknown</td>
<td>Boyd.</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>Sensitive and Inflammation</td>
<td>Anti-Muscle</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Metalloids?</td>
<td>Various</td>
<td>Boyd.</td>
</tr>
</tbody>
</table>
with antibody, may destroy it in two ways. Firstly, it may render the cell susceptible to lysis by the complement-proteolysis lysing systems, and secondly, it may lead to opsonization and subsequent phagocytic destruction of the cell. The first mechanism can be demonstrated in the autoimmune hemolysis anemia, and complement-fixing antibodies are commonly found in autoimmune diseases. The second mechanism has been demonstrated upon tumour cells growing as peritoneal implants of previously immunized mice. We must take into account, however, that these phenomena occur because the cells themselves may be defective in constitution.

Present lines of investigation are mainly concerned with examining the hypersensitivity reaction. Those who have provoked autoimmune disease in experimental animals have generally done so by inducing a hypersensitivity reaction, concurrent with the injection of tissue antigen, by injecting Freund's adjuvant which consists of a suspension of dead mycobacteria in oil. Such treatment is by no means always successful but the required results are obtained in a fair majority of cases. The evidence for hypersensitivity reactions operating in autoimmune disease is indirect, but is substantiated with a number of suggestive observations. Auto-immune phenomena have been reported in cases of anemias, globulinemia and in such cases obviously cannot be due to circulating free antibody. Passive transfer of serum does not precipitate autoimmune disease, and there is a corresponding lack of correlation between antibody titre and the severity of the lesion. Experimental support for these last two observations and the conclusion they imply, has come from two sources. Firstly, it has been shown that auto antibodies alone will not cause suppression of splenomegaly unless there is tissue damage as well. It is well known that mice with splenomegaly due to inoculated brain tissue often show no antibodies at all despite the progressive nature of the lesion. The last point is indicative of the hypersensitive state encountered in autoimmune disease as the response of the auto-immune disease states to steroid therapy. These agents will also reduce the hypersensitive state both in experimentally induced, and in naturally acquired reactions. They will also control any inflammatory response to a large extent no matter what their etiology may be.

Suggestive evidence for tissue damage as a sequel to intravascular conglutination of red cells, with intra-embolic formation, has been found in many blood diseases, not all of them auto-immune, and in systemic lupus erythematosus, where small vascular lesions are said to give rise to small areas of hemorrhage and necrosis in the skin. Some of the clinical phenomena in other diseases of a possible autoimmune nature may be suggestive, but anti-red cell conglutination are rarely found.
The direct cytotoxic action of antibodies has not as yet been demonstrated although Bailey et al. sought this action specifically in the presence of female rat ascites and homologous heart tissue. One point that has emerged definitely from this work is that the placenta may protect the fetus from the hypersensitivity reaction in the mother perhaps by virtue of the high histamine content.

Certain additional factors may also play some part in disease which have as their basis some immunological incompetence. The first is production of a haemato-protein antigen complex which then combines with its specific antibody to form a toxic product. This conclusion is by inference from observations on drug sensitivity states and from the work of Masugi et al. in glomerulonephritis. Burnett also supposes damage to the cell by local contact with an immunologically competent cell carrying the specific antibody. This useful opinion was based upon the observation that lymphocytes from an immunized animal showed specific adhesion to those humour cells with which the animal had been immunized. This can also work the other way, damage to the immunologically competent cell resulting from contact with antigen in its soluble or cellular form. Further damage may be done to neighbouring cells and to the body as a whole by the release of toxic products from the immunologically damaged cell. Reference is this will be made later in discussing systemic lupus erythematosus.

The bulk of the evidence suggests that antibodies to normal tissue cannot alone cause any disease in these tissues. Isla and Hark have described autolysin factor in the blood of an infant whose mother had systemic lupus erythematosus. The role of antibody in this antibody in the blood shows that it was not reacting with the infant's tissue. The cause of causation of the hypersensitivity reaction is therefore transferred to the lymphocyte. Hyper hypersensitivity to tuberculin may be passively transferred to agamma globulinemic people by transfusion of lymphocytes. Moreover, it has been shown that homograft rejection does not take place unless lymphocytes are allowed access to the graft. It is possible in the face of this evidence that Jones' virus report a successful skin homograft to an agammaglobulinemic child.

The true quest in auto-immune studies is to reveal those mechanisms by which auto-antibodies come to be formed in the first place. If tissue damage is the primary lesion, then autoantibodies will be formed to those products of the damaged tissue which come into contact with the R.E.S. The virus, with its outstanding ability to multiply recognize one to hype cells, comes immediately to mind. The Istell type of "virus" as a polymer of DNA or RNA which is capable of intracellular replication by this definition a virus may arise from a great
or chromosomal defects in a cell. Antibodies to liver tissue are found in viral hepatitis and also in experimental carbon tetrachloride poisoning. Hypothyroidism induced systemic lupus also gives rise to a multiplicity of cellular autoantibodies.

On the other hand the autoimmune and the primary autoantibodies we must examine the faults by which they arise. Green describes the following hypothesis: In the first, a foreign protein in the tissue subsequent to infection, injection or chemical damage gives rise to antibody whose antigen specificities are not of normal cells. The resulting immunological reaction is responsible for the observed tissue changes. The second mechanism involves an antibody reaction with the patient's own cells made antigenic by some alteration in their constitution. Green's view is that an abnormal immunologically competent cell reacts with that damaged normal tissue.

Most of these explanations are at the present time completely unacceptable, mainly because of the lack of experimental evidence. To pursue the last view expressed Green suggests that an immunologically competent cell and the ability to form autoantibody somehow escape destruction during the phase of increased susceptibility to auto-antigen, and that its descendants all inherit the rogue ability to manufacture the same auto-antibody. This theory has many weaknesses, but it has one interesting aspect, and that is the implication of a breakdown in one of the mechanisms of self-regulation. Such an interpretation places the somatic mutation theory of cancer. Failure in this mechanism was reported by P. Jacobs, W.T. Bent Brown et al., to operate in cases of chronic myeloid leukemia. Chromosome identification techniques showed the emergence of successive clonal of abnormal white cells after suppression of the previously dominant clone by appropriate chemotherapy, the suggestion being made that these cells somehow escaped a normal destruction in the bone marrow.

We are led by this conclusion to consider the part played by the immune response in the cellular regulation of the body. I would propose the constant emergence of potentially neoplastic mutants in the cell population which are recognized as mutagenic and destroyers by immune reactions before they have time to multiply. Radiation would predispose to malignancy by increasing the mutation rate, local irritants and chemical carcinogens acting possibly in the same way. An autoimmune disease tissue damage may result in normal tissue from overactivity of the same system, in humour growth, stimulating, or failure to eliminate all neoplastic cells. Robertson et al., have found evidence of lack of normal levels of proopio in people with carcinoma of the skin.

Like the tendency to develop cancer, the predisposition to auto-immune disease is to some extent hereditary. The parents of patients with autoimmune thyroiditis show a higher
existence of thyroid disease than is evident in the population at large. 

Goides 30 reports that autoimmune thyroiditis predisposes to the development of thyroid carcinoma. This may be due to the common defect I proposed, or to the immunity of tumour cells to destruction by thyroid auto-antibodies present in the disease. These tumour cells can be shown to lack a specific auto-antigen present in normal thyroid cells. This aspect of autoimmunity is certainly deserving of further study, but as one progresses the subject becomes more complex and it is doubtful if our knowledge is far enough advanced to pursue this kind of concept further.

However, observe the pathology of autoimmune disease. The clinical and pathological features associated with them are well known. The autoimmune disease for excellence is Hashimoto thyoiditis. It is supposed to be a reaction of the K.E.S. to previously sequestered thyroglobulin which has escaped the thyroid follicles. The disease is characterised by a painful enlargement of the thyroid gland and a raised E.S. Auto-antibodies to thyroglobulin and thyroid cell factors may be demonstrated in the serum, and occasionally i.e. cells are found. Pathologically there is gross fibrosis of the gland, and histology shows a heavy lymphoid infiltration and establishment of germinal follicles within its substance. Abundant plasma cells and fibroblasts are seen, but towards the end the picture is one of complete fibrosis with a few isolated thyroid follicles remaining. It is interesting to observe that until the terminal stages of destruction of the gland the patient usually remains euthyroid.

Smart and Allen 33 have shown that fragmentation of the basement membrane of the thyroid follicles occurs in hyperthyroidism. Many people believe that a transient hyperthyroid state precedes the development of autoimmune thyoiditis, whereas we prefer to regard the escape of thyroglobulin as a consequence of some other, possibly infective, process. Because the K.E.S. has never been encountered free thyroglobulin during the stage of immunosorbability, it forms antibody to it and the disease becomes established. 34,35

Like many simple explanations this is most certainly not the whole truth. Damage to the thyroid with release of sequestered antigen does not result, experimentally, in autoimmune thyroiditis. This can readily be produced by employing an adjacent connective tissue damage to the gland.

Goides is of the opinion that thyroglobulin leakage occurs normally, and that the disease must be a reflection of some underlying disorder of the K.E.S. Leakage of thyroglobulin has been demonstrated by the use of the radioisotope 33 in normal animals and we cannot find a hypothesis, in the face
of such evidence, which readily explains all the observed phenomena.

The primary disorder may be in the cells themselves or in the
dialoged in they manufacture, and this may conform to a possible
genetic basis for the disease.

The rheumatoid group of autoimmune diseases occupy a place near
the other end of the spectrum. Rheumatoid arthritis presents a puzzling
picture. It is now recognized as being a generalized disease with
a strong hereditary suspicion, due to its thought to be a single autosomal
dominant. Active rheumatoid arthritis is characterized by low fever,
wasting, and a polyarthritis. Anemia, eye disease, which can often be
very acute, and skin rash, complete the picture. The disease may
be associated with ulcerative colitis, psoriasis, and infections, the
most significant being PPD organisms and the streptococci. (14) The "infective"
type of rheumatoid arthritis shows a lower incidence of positive
sensitive slide-cell agglutination test than the autoimmune type.

Psychological or infective stresses may serve to "trigger off"
in an attack, and there is a well known association between
the complaint and the weather. The fever, anemia and wasting of
rheumatoid arthritis lead to the discovery of immune auto-antibodies
in the serum. The auto-antigen in the case appears to be denatured
gamma globulin resulting perhaps from a previous anti-globulin reaction.
(11, 12) The R.E. cell phenomenon is also quite frequently observed. Lymphocytes
or a normal rheumatoid arthritis will cause symptoms of the disease
in an uninfected recipient. (13)

Rheumatoid arthritis has been described in cases of agamma
globulinemia, and this seems to indicate that the multiplicity of
soft cell auto antibodies found play little part in the causation of
the disease. (6)

The other member of this group which draws attention is
the disorder of systemic lupus erythematosus. Immunologically
it is similar to rheumatoid arthritis, but the main features are clinically,
confined to the soft tissue, not the bones and joints. Recent work
by S.L. Corman et al. (37) supported by the work of Weisman and Thomas,
has provided a reasonable and very intriguing hypothesis of the
possible etiology of systemic lupus erythematosus, and no apology
is made for devoting considerable space to it.

The basis of this hypothesis is that the lymphocytes
in the cytoplasm in suspension in R.E. serum are unable to
resist the changes in pH subsequent to phagocytosis. As the intracellular
pH falls from 7 to 5, these lysozyme enzymes liberating the enzyme
deoxyribonuclease which is then free to attack the cell nucleus. If
the nucleus depolymerization takes place and subsequent death of
the cell. The disturbed nucleus is extruded, and subsequently
phagocytosed by a polymorph to form the typical R.E. cell.
The cytoplasm of the nucleus of the dead cell act as foreign antigens and give rise to one nuclear factor and other antibodies which constitute the 13 serum. The phagocytic cell which removes the damaged cell and nuclear components is liable to exactly the same fate as its predecessor as the intracellular lactate rises and the pH falls. The process is evidently self perpetuating and once the primary agent be it infected or whatever, has begun the process will continue in its absence. Hyaluronate induced SLE reverse once the autologous antigen has been neutralised. It is a feature of the "collagen" diseases that hypersensitivity to nucleotide polymers is common. I think it interesting that the best experimental method of demonstrating LE cells is not an immunological one, and that cells very like LE cells may be seen in the normal bone marrow smear.

The haemolytic anemia from the most readily studied of all the autoimmune diseases, because of the availability of material to study. The autoimmune type of haemolytic anemia is generally a secondary or acquired haemolytic anemia. The disease is characterised by an acute destruction of red cells, or "mais" often following a viral infection or a vague period of ill health. The serum contains weak or incomplete antibody which agglutinates both the cells of the patient and some of the normal individual. This antibody is often to one of the rheum antigens, usually 
intermediate, but the majority of sera react with a pattern common to all human red cells. The cells themselves are coated with a globulin antibody which can be detected with anti-human gamma-globulin serum, the Coombs test. The antibody coated cells often assume a spherocytic nature. The destruction of the red cells may be extravascular or splenic, but the mechanisms are probably similar to those by which autoantibodies cause the destruction of incompatible red blood cells. Both cells and serum antibodies are lysed by the complement lysic system. The function of the antibodies may well be to render the cell more susceptible to phagocytic destruction in the spleen. There is a well authenticated report of a haemolytic type of anemia in an agammaglobulinaemic cured by reaction of the spleen. This was a pure case of hypersplenism but this trait must be present in all those with autoimmune haemolytic anemia who benefit by splenectomy. (11)

Rheumatic fever has often been held up as an example of autoimmune disease, but according to Waksman the best experimental evidence show that Auto-immunization plays a very minor role in the aetiology of rheumatic fever. The causation of rheumatic type lesions by injections of homologous heart tissue has not been confirmed in.
Diagram of the L.E. cell phenomenon

after A. S. Scarr, et al.

Bacteria → phagocytosis in L.E. serum. → Metabolic changes
Viruses
Fungi
Biological

pH 7.

Lactic acid produced rises
Oxygen consumption rises
Substrate utilization rises

pH falls to 5

Granules disrupt

Liberated desoxyribonucleic dephosphorylates nucleus

Plasma cell: antibody formation

Neutro

Cell with disturbed nucleus

L.E. cell

Polymorph

pre. L.E. cell
Loombs test: From Wintrobe.

<table>
<thead>
<tr>
<th>Haemolytic Disorders due to</th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Sphaerocytosis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Autoimmune haemolytic anemia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>1. Without serum antibodies</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2. With serum antibodies</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Isoimmune (erythroblastosis fetalis)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Physical or Chemical agents</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxysmal cold haemoglobinuria</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Among the latest additions to the already impressive list of auto-immune disease is pernicious anaemia. It was recognised that idiopathic achlorhydria disease was frequently associated with pernicious anaemia. Examination of the gastric mucosa of patients with pernicious anaemia revealed heavy lymphocytic infiltration, and this led eventually to the immunological theory of the disease. Anti-intrinsic factor antibody and antibodies to parietal cell cytoplasm were found, and also, in many cases, anti-thyroid antibodies. Using this discovery, Hamburger proposed the theory of a non-specific, or general, auto-immune reaction, with antibodies to many organs, but the disease being manifest in one tissue only. Irvine thinks that this phenomenon can be explained by supposing a closer general upset in immune tolerance. It has still not been proven, however, that the presence of antibodies to a tissue will cause disease in that tissue.

Smitten has pointed out that in the malignant lymphomas and tumours of the RES., many suggestive immunological changes may be demonstrated. In Hodgkin's Disease, leukopenia, lymphopenia, fever, anaemia, and skin changes are all suggestive of a disorder of the immunological processes. Leukocytosis, and anti-red cell antibodies are found frequently, and also anti-nuclear factor occasionally. There is a strong suspicion that Hodgkin lymphosarcoma, lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, and histiocytic leukemia are all separate manifestations of the basic disorder. In each of these diseases auto-immune phenomena have been described. In some cases the nature and extent of the lymphoid changes is unknown. The influence of these changes is probably mediated by antibodies to normal lymphoid cells. Evidence supporting this hypothesis is indirect, but multiple infections with poor immune response, the prolonged survival of homografts, and the influence of steroids all suggest that something of the sort may indeed take place.

In many kinds of liver disease, liver cell auto-antibodies can be found. An auto immune disease has been suspected in hepatitis hepatic cirrhosis, and in progressive hepatic cirrhosis which may follow viral hepatitis or other diseases of the liver. The position is not clear in liver disease. Occasionally anti-liver cell auto-antibodies may be demonstrated in obstructive jaundice, toxic jaundice, and necrosis involving the liver, and this seems to indicate that any process which damages the liver cells can give rise to such auto-antibodies. This has been shown to be so in rats.
processed with carbon tetrachloride. Despite the rising levels of anti-liver cell antibodies after the liver damage no subsequent disease could be attributed to them. The function of these antibodies may be to protect other cells in the body from toxic products released from the damaged cells, by neutralizing of the harmful fragments. This may account for the occasional it, tell seen in these liver diseases.

There are many autoimmune diseases which could be discussed further, but the selection already mentioned is fairly representative. Many interesting topics remain to be discussed, such as the significance of eye change in sympathetic ophthalmia, arthritis, granulomas and leukemoid arthritis, but in the space remaining I would prefer to mention the homograft reaction, and point out in what fields of application its study will be of use.

The homograft reaction occurs when tissue is transplanted from one individual to another not antigenically related. In experimental work the transplant is usually of skin, but as a wider specialized line of investigation lymphoid cells and cells of bone marrow are sometimes used.

The rejection of a skin transplant does not occur until the graft has become vascularized. The tissue around the graft then becomes heavily infiltrated with lymphocytes around a line of demarcation, and these then invade the graft itself and destruction of the graft cells. The host can tissues react with a fibroelastic proliferation and a non-specific inflammation and resulting granulation tissue formation. In about 2 to 4 weeks the homograft “calcs” off and healing of the graft area takes place. The reaction can be halted by irradiating the graft area before or after placing the graft. Any grafted tissue will be rejected by a similar mechanism. Steroids will prolong the survival time of a graft, and adrenalectomised animals will reject it more quickly.

The grafting of blood cells or of lymphoid tissue can have several different effects, depending upon the circumstances of the host. Grafting of this kind however is always followed by a generalized disease, or homograft disease. Secondary disease, runt disease, and wasting disease are all separate aspects of homograft disease.

Secondary disease is caused by “grafting” live marrow cells from a healthy animal to an immunized one. Such grafted cells will “take” and form enough red cells to prevent death from aplastic anemia, but in 2 weeks or so the host develops lymphoid atrophy and weight loss which may lead to eventual death. At this point it will tolerate a skin
graft from the donor animal. Cure and graft rejection occur when the animal is reinforced with identical bone marrow cells. The severity of secondary disease depends upon the amount of irradiated host recepive and the "dose" of donor cells grafted.

Host disease is very similar to wasting disease in the appearance of wasting, lymphoid atrophy, and tolerance of donor grafts. It is precipitated by the injection of marrow, or lymphoid tissue from homologous adult donor animals into newborn, or very young, mice. Biomechanical explanation of the cause of the disease is that the new born animals' lymphoid tissue is immature and incapable of forming antibodies, while the mature donor cells are capable of destroying the host tissue unopposed.

Wasting disease occurs when parental hematopoietic cells are injected into irradiated or newborn mice of the F1 generation. It is similar in all respects to the other diseases described. Unirradiated will protect mice to some extent from the homologous diseases.

Each of these conditions has a definite immunological basis, and they have a practical significance for the surgeon who wants to transplant kidney, and the physician who wants to give a new bone marrow to the person who has exhausted his own. Biomechanical theory of the incompetent and competitive phases in the development of the lymphoid tissue gave little hope of ever making a permanent and lasting beach in the barrier of tissue transplantation. It has now been shown that the immune response in the newborn mouse is different from that of the adult only in a quantitative respect. It was there, but required a sensitive test to uncover it.

Hy Howard and D. Mitho used as a test the weight of the spleens of animals with experimentally induced renal disease. They sought to prevent this disease by using a killed vaccine of irradiated cells from the spleen of a donor animal. Protection was optimal at a dose of about 10^6 cells, larger doses than this produced an aggravation of the disease, in fact a type of immunological paralysis analogous to that reproducible in animals by very large doses of pneumococcal polysaccharide. The ability to produce immunity and "tolerance" (immunological paralysis) in the same experimental system leads us to a simpler concept of the mechanism of homologous disease. The resistance of the adult animal to induced tolerance seems related to be a function of the amount of lymphoid tissue present and the quality of that tissue. It is an easy conclusion that tolerance to a homograft may be readily induced in the adult by diminishing the amount of tissue capable of reacting and the homograft. Once tolerance has been induced, it will
not be realised, but a criteria will have been created. Tolerance is achieved in the adult by reducing the lymphoid tissue with drugs and by irradiation.

It seems that I have strayed far from the narrow path of relevance in discussing the homograft reaction, but I hope to return back to the original topic by examining the similarities produced by these tissues, and those of an immunological origin.

The main feature of homograft reaction is a profound lymphopenia, with loss of lymphocytes from the lymph nodes. The reticulum is left more or less intact. This is somewhat similar to the picture observed in adenecatectomised rats stimulated or persistently by injections of Freund's adjuvant, before production of lymphocytes and plasma cell occur. What is in fact being produced is a "stress", and the subsequent lymphopenic has in the past been attributed to an increase in the secretion of the adrenocortical hormones. Experimentally, it may be shown that steroids do inhibit the metabolism of lymphoid cells, both in vivo and in vitro. But in the adenecatectomised animal, how can this mechanism operate?

Many of the auto-immune diseases and also the homograft reaction can to a large extent be halted by steroids administered, yet the auto-immune disease may be exacerbated by stress of a psychogenic or infective nature, where the steroid secretion would by all accounts be increased. This apparent paradox is worthy of a letter solution than I could propose.

Placing a homograft in contact with exposed animal tissues may provide a similar insult to the body as would the presence of dead mycobacteria. From the point of view of organisation, the homograft would lack the specific adhesin properties of the cells with which it was in contact, and hence these tissues would modify their response. One would expect the adjacent cells to ignore the foreign invader and carry on with the healing process as though it did not exist. The adjacent cells however unite with the homograft, and until the arrival of the lymphocyte, treat it as normal tissue. The lymphocyte therapy must be that cell which is able to modify the response of the tissue with respect to another. What gives the lymphocyte this ability, and how is it controlled? As in so many aspects of immunity these questions cannot at present be answered. That the solution to them if eventually found will enable us to treat and cure the auto-immune diseases must be an augury of hope for the future.

To summarise briefly, the content of this essay. The cells and substances concerned in the immune response are discussed,
and the functions of the immune mechanisms of the body are set forth.

The criteria for identification of an autoimmune disease are given and
the possible mechanisms which may be involved in the production of
close diseases are examined. The features of several autoimmune
diseases are described, with a word about the homologous diseases
and the humoral reaction. The last part presents several questions
of general importance in relation to the control and function of these
reactions in the normal body.

To conclude I must say that there are many topics relating to the
immunological processes of the body which I have not the space
to present. Much of the material set down is irrelevant and many
of the newer generalities irritating, because my purpose is not to
appear superior, in respect of knowledge or judgment, to my fellows,
but to satisfy the part of myself, called curiosity, that is
never satisfied. To many others, as to myself, the subject has provided
a "look and ye shall pay" challenge, in which evidence to quote
in support of one own ideas is readily forthcoming. If this is in
some aspects comforting, it is, in the main, discouraging, because it
indicates how far away the solutions of these deeper problems rest.

The easiest conclusion to draw is to suggest that these
problems will occupy the most able of minds for many years to
come.
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