Auto-Immunity

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 all 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 proposition experimentation and verification. From the start the medical scientist is confronted by complexity, and, from clues provided by investigation, the final solution is found in a retrograde manner.

In the manifest impossibility of starting from simple precepts lies the inherent weakness in medical investigation, and, in addition to this, there are few rules which can be used to guide the enquiring mind. Therefore it is inevitable that mistakes shall arise, and the problem become ~~masked~~ obscured with confusion, before the paradoxes 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 conclusions, but rather I have devoted it to a very general survey of the subject with a few comments and intrusions upon interesting points.

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

Before discussing those defects to which the immunological processes are subject, it is necessary to survey the mechanisms involved. The main functions in 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 beginnings of disease.

Detrimental	Beneficial.
Local tissue reactions	Defence against invaders
Systemic hypersensitivity reactions	Embryological organisation
"Auto-immune" disease.	Adult "Homeostatic" functions
	"Integrity"

The cell is the basis of all immunological phenomena. All the cells in the body participate, to some extent, in immunological processes, but the onus of initiating and regulating these responses lies with the cells of the reticulo-endothelial system, hereinafter referred to as the R.E.S. 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 distribution. Almost certainly these two groups stem from one type of cell, the primitive reticulum cell found in lymph nodes, thymus, spleen and bone marrow.

An associate of the reticulo endothelial cells, implicated in certain phenomena consequential to local tissue sensitivity reactions, the mast cell or histiocytic basophil, must be mentioned. It is found in close association with blood vessels in superficial tissue, and is responsible, by means of the histamine, proteases, peptides, and serotonin it releases, for the vascular phenomenae seen in such reactions.(40)

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 "scavaging cells of the body" from their ability to ingest dead tissue and bacteria.

Lymphocytes are formed from "primitive" reticulum cells in the lymph nodes, thymus, and spleen. They may be seen in association with those 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 lymphocytes from thoracic duct 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 capeable of division under special circumstances.(3) The lymphocyte is capeable of mild phagocytosis, more a pinocytosis, and amoeboid movement. Peculiar to these cells is their ability to enter and leave other cells of the body at will.

In addition to lymphocytes the R.E.S. 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 commented upon later.

Allied to, but not synonymous with the R.E.S 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 be it free or fixed is capeable 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 haemocytoblast to the normoblast 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 R.N.A" 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 transitory 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 somatic mutability at some period during antigenic stimulation, or at some time during embryonic life; enough, in fact, to provide a range of clones capeable of reacting with all foreign antigen patterns.(2, 13, 35)

The essential difference between Burnets' 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 embodies the essentially Lamarkian concept of the mesenchymal cell being able to modify its antibody producing pattern or gene in the presence of a suitable antigen. It is now believed that the second process is the one which occurs. In a simple organism, like paramecium, observations have shown the ability of the single cell to vary its constitution to suit environmental conditions.(4)

In either case there should be, unless our premises are false, some mechanism by which the R.E.S "recognises" the cells which surround it as "self" and does not thereafter form antibodies to them. It has been suggested that this first takes place in the thymus, and from here subsequent colonisation of the body's lymphatic tissue takes place.(24,35) The thymus gland is capeable of considerable hyperplasia during antigenic stimulation, with formation of pseudo glandular acini, lymphoid follicles, and plasma cells. Mast cells and eosinophils also appear, giving the typical appearance seen in the thymus during the course of experimental auto immune

disease in rats.[29]

Lymph nodes, draining the antigenically stimulated area, become rich in plasma cells, and produce a polynucleotide substance which will increase the reticular cells in lymph nodes and spleen of adrenalectomised rats, with a drastic reduction of the production and maturation of lymphocytes and plasma cells in the thymus and lymph nodes elsewhere.[29] Hodgkins lymphadenoma often produces a similar histopathological picture of reticular hyperplasia and lymphopenia.

The antibodies produced by the plasma cells are found in the γ globulin fraction of the plasma proteins. They are glycoproteins of a molecular weight 160 - 180 thousand and an isoelectric point at pH 6·7 - 7·3. In the range of body pH therefore they preserve an electron "balance" and are therefore not susceptible to spacial distortion by unbalanced electron charges. The shape of the molecule determines its antigenicity and this it keeps very well in spite of rough chemical treatment. Up to 3/4 of the molecular weight may be lost without spoiling this specific spacial relationship.

Most of the γ 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 ~~antigenically~~ active protein by the plasma cell, or antibody formed to "rare" antigens, such as the polysaccharides of some plants, or to inert antigens with crystalline patterns which could stimulate antibody formation, like silica or asbestos.[1,5,8]

The function of antibody is to coat the foreign antigen rendering it chemically inert, to provide a "sticky" surface facilitating phagocytosis (opsonisation) and to induce lysis of the complex with eventual enzymic destruction.

In this 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 9×10^5. 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 defence mechanism of the body, but so little is known about them it would be dangerous to suppose they have no other function.[6,8,9,10]

The functions of the reticulo endothelial 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, with a rising titre of antibody to the organism or its products, local tissue responses at the sight of invasion, and a hypersensitivity reaction, sometimes called the delayed response, which may be allergic in character.(7) This last response is a feature of the main granulomatous conditions, syphilis, tuberculosis, leprosy, and the mycotic infections, and is present in the "autoimmune" diseases. Here one must remark upon the similarity, both immunologically and clinically, of the infective granulomata 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. Here a direct bacterial challenge to the body is met with a type of reaction in which the organisms and the body's cells themselves are destroyed indiscriminantly. Diagnostically the auto immune diseases resemble these granulomata; at one time it was thought that discoid lupus erythematosus was a cutaneous tuberculoid infection. Moreover the ability of dead mycobacteria, used as an adjuvant in experimental induction of autoimmune disease, to cause sensitisation to the injected tissue antigens, is probably a reflection of their curious effects when causing disease in the natural state.

The other functions of the immune response exceed the simple defence of the individual. Embryologists have seized upon the antigen - antibody response to provide a model for the explanation of embryological organisation. 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 developemental neighbour. He 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 leukemia is essentially a failure to prevent abnormal cells of the marrow proliferating, and that auto-immune 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, 38, 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 present lines of enquiry seek to establish wether or not this is the case; does a perturbed R.E.S attack the tissues of its own body, or are the immunological features of auto immune disease merely a reflection of some unknown and hitherto unsuspected disorder? Whatever the ultimate outcome of this enquiry, the immunolog. 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 auto-immune disease, it is agreed that certain criteria should be satisfied. Those given below I owe to Witebsky.[33, 34, 3]

i) Demonstration of free circulating antibodies active at body temperature, or the demonstration of cell bound antibodies by direct means.

ii) Recognition of the specific antigen against which this antibody is directed

iii) Production experimentally of antibodies against the same antigen in experimental animals.

iv) 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 verification in every case of auto immune disease, certainly those in which the specific antigen or antigens are not known. Those diseases at present suspected or "proven" to be of auto-immunological aetiology are shown in the table opposite.

It can be seen from this table that the auto-immune diseases form a spectrum from extremly 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 (eg serum immuno conglutinin) or antabodies of low specificity are encountered.[33]

The prescence of antibody to a tissue may theoretically damage that tissue in a number of ways. These are, briefly, an Arthus type of reaction, resulting in vascular damage to the organ concerned, a delayed hypersensitivity reaction, a direct cytotoxic actoin, and disseminated vascular damage by intravascular conglutination by red cell antibodies, and the indirect cytotoxic action.[3]

There is evidence that an Arthus type of reaction may lead to homograft rejection (although this is scarcely an auto-immune 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

The Autoimmune Diseases (after Burnet[75])

Disease	Nature of Antigens	Nature of Antibody	Reference.
Disease involving sequestered antigens.			
Hashimotos Disease	Thyroglobulin	Antithyroid A.I.C.F.	Weir Davies et al.
Idiopathic Addisons		Antiadrenal : Thyroid	-
Disease	Unknown	auto-antibodies. A.I.C.F.	
Sympathetic Opthalmia	Lens antigens	Anti-lens Antibodies	J. Gear.
Sjögrens Disease	Probably a General disturbance	A.I.C.F. A.N.F.(LE cells).	B.R. Jones, W.G. Boyd.
Peripheral neuritis	Unknown	A.N.F. ?	L. Illis.
Sterility :(male).	Unknown	A.I.C.F.	-
Disease associated with common antigens	A I C F = Autoimmune complement fixing factor. A.N.F. = Anti-nuclear factor.		
Rheumatoid Arthritis	Denatured γ globulin Infective agents	A.I.C.F. A.N.F. LE cells Rose Waler factor False + Wr reaction Anti-red cell antibodies	G.D. Kersley, D.M. Weir, E.J. Holborow et al.
Systemic Lupus Erythematosus and Discoid Lupus.	Nuclear & cytoplasmic components, Platelet factors, Leukocytes.	A.I.C.F. A.N.F. (LE cells) Rose Waler Factor False + Wr. Anti-red cell, Antiplatelet, Antiglobulin Anti leukocyte agglutinins.	J.S. Beck. Weir et al Burnet. Wintrobe, B.R. Jones etc.
Acquired Haemolytic Anemia (auto-immune)	Red cell surface antigens Rhesus antigens	Anti rhesus, red cell agglutinins (warm & cold).	Wintrobe.
Idiopathic thrombo-cytopenic purpura.	Platelet antigens	Anti platelet (agglutinin?)	Wintrobe W.C. Boyd. Irvine, Davies et al.
Pernicious Anemia	Intrinsic factor. Gastric mucosa. Parietal cells.	Antimucosal anti-intrinsic factor. Anti P-Cell. Antithyroid. A.I.C.F.	Davies et al. Markson & Moore Roitt Taylor et al.
Myasthenia Gravis	Nuclear component	A.N.F.	White & Marshall
Iron deficiency anemia	mucosa ? Marrow cells? red cells?	None demonstrated.	Markson & Moore
Chronic Hepatitis (Not infective)	Breakdown products of liver cells.	Anti liver: A.I.C.F. A.N.F. LE cells occasionally	Holborow & Johnson et al.
Infantile cirrhosis	Breakdown products of liver cells.	Positive T.R.C tests.	Pranranjan Prasad.
Hodgkins Lymphadenoma	Abnormal lymphocytes?	Unknown : ANF and Anti red cell antibodies	Kaplan & Smithers.
Secondary Autoimmune Disease.			
Sedormid Thrombocytopenia	Drug-platelet complex	Anti-platelet agglutinin	Wintrobe
Post cardiotomy syndrome. post myocardial infarction syndrome	Myocardial cell components.	Anti-myocardial C.F. Antibody	Cecil and Loeb.
Hydralazine Syndrome	Drug-protein complex?	As for S.L.E.	G.D. Kersley.

Disease	Nature of Antigens	Nature of Antibodies	Reference.
Rheumatic fever	Streptococcal products Protein or Polysaccharide?	Anti-Myocardial.	Kaplan & Myasserian Lancet 1 706 1962.
Ellis type I Glomerulonephritis	Streptococcal products.	Anti-glomerular.	W.C. Boyd: Masugi.
Myopathies, neuropathies and anemias in Malignant disease, especially Lymphomas.	Unknown	Various.	Kaplan & Smithers.
IV Experimentally produced Phenomena resembling Auto-immune disease.			
Experimental glomerulonephritis (Masugi)	Glomerular fraction of Homogenised Rabbit Kidney	Anti-glomerular Globulin	W. Boyd.
Mouse Encephalitis	Brain + adjuvant	A.N.F. Anti-myelin and anti-brain antibodies.	W.C. Boyd J. Lear.
Homologous disease Homograft reaction Possible	cells of host animal grafted cells	Various A.N.F. and others	Kaplan. Kaplan & others.
V Auto immune diseases Not yet proven.			
Multiple sclerosis	Myelin or precursors.?	Anti schwann cell?	W.C. Boyd. Kaspary et al.
Ulcerative Colitis	Milk proteins? mucosal factors?	Anti lactalbumin " casein " lactoglobulin	Taylor and Truelove.
Polyarteritis Nodosa	connective tissue	unknown	W. Boyd
Dermatomyositis	connective tissue	unknown	W. Boyd
Malabsorption Syndromes	Gluten and Metabolites?	Anti-Mucosal antibodies?	-

with antibody, may destroy it in two ways. Firstly it may render the cell susceptable to lysis by the complement or properdin lysis systems, and secondly in may lead to opsoniation and subsequent phagocytic destruction of the cell. The first mechanism can be demonstrated in the autoimmune haemolytic anemias, 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 immunised mice.[43] 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 auto-immune disease in experimental animals have generally done so by inducing a hypersensitivity reaction, concurrent with the injection of tissue antigen, by injecting Freunds 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 auto immune disease is indirect, but is substantiated with a number of suggestive observations.[3] Auto-immune phenomena have been reported in cases of agamma-globulinaemia and in such cases obviously cannot be due to circulating free antibody.[6, 3, 27] Passive transfer of serum does not precipitate autoimmune disease, and there is a corresponding lack of correlation between antibody titres and the severity of the lesions. Experimental support for these last two observations, and the conclusion they imply, has come from two sources. Burkey showed that auto antibodies alone will not cause sympathetic opthalmia unless there is tissue damage as well. It is well known that mice with encephalomyelitis due to innoculated brain tissue often show no antibodies at all despite the progressive nature of the lesion.[3] The last point indicative of the hypersensitive state encountered in auto immune disease is the response of the auto-immune disease states to steroid therapy. These agents will also reduce the hypersensitivity 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 aetiology may be.[1]

Suggestive evidence for tissue damage as a sequal to intravascular conglutination of red cells, with micro emboli formation, has been found in many blood disorders, not all of them auto immune, and in systemic lupus erythematosus, where small vascular lesions are said to give rise to small areas of haemorrage and necrosis in the skin. Some of the clinical phenomena in other diseases of a possible auto immune nature may be suggestive, but anti red cell conglutinins are rarely found.[11]

The direct cytotoxic action of antibodies has not as yet been demonstra although Cawley et al sought this action specifically in the foetuses of female rats sensitised with homologous heart tissue.[32] One point that has emerged indirectly from their work is that the placenta may protect the foetus from the hypersensitivity reaction in the mother, perhaps by virtue of the high histaminase content?

Certain additional factors may also play some part in diseases which have as their basis some immunological incompetence. The first is production of a haptene-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 on glomerulonephritis. Burnet also supposes damage to the cell by its contact with an immunologically competent cell carrying the specific antibody. This useful opinion was based upon the observation that lymphocytes from an immunised animal showed specific adhesion to those tumour cells with which the animal had been immunised.[3] This can also work the other way, damage to the immunologically competent cell resulting from contact with antigen in its soluable 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 to 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 those tissues. J Swanson Beck and N.R Rowe describe antinuclear factor in the blood of an infant whose mother had Systemic lupus Erythematosus. The rate of decline of this antibody in the blood showed that it was not reacting with the infants' tissues.[9] The onus of causation of the hypersensitivity reaction is therefore transfered to the lymphocyte.[6,7] Hypersensitivity to tuberculin may be passively transferred to agamma globulinaemic people by transfusion of lymphocytes.[6] Moreover Gorer has shown that homograft rejection does not take place unless lymphocytes are allowed acess to the graft.[39] It is puzzling therefore in the face of this evidence that Good & Varco report a sucessful skin homograft to an agammaglobulinaemic child.[6]

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 auto-antibodies 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 incognito and to lyse cells, comes immediately to mind. Here I shall define "virus" as a polymer of D.N.A or R.N.A which is capeable of intracellular replication: by this definition a virus may arise from a genetic

or chromosomal defect in a cell. Antibodies to liver tissue are found in viral hepatitis and also in experimental carbon tetrachloride poisoning. Hydralazine induced systemic lupus also gives rise to a multiplicity of cellular autoantibodies

If on the other hand the auto-antibodies are the primary aetiological agents we must examine the faults by which they arose. Gear describes the following hypotheses.[34] In the first, a foreign protein in the tissues subsequent to infection injection or chemical damage gives rise to antibody whose antigenic specificity overlaps with that of normal cells. The resulting immunological reaction is responsible for the observed tissue changes. The second mechanism involves an antibody reaction with the patients own cells made antigenic by some alteration in their constitution. Burnets view is that an abnormal immunologically competent cell reacts with and damages normal tissue.[2,13,35]

None of these explanations is at the present time completely acceptable, mainly because of the lack of experimental evidence. To persue the last view expressed Burnet supposes that an immunologically competent cell with the ability to form auto-antibody somehow escapes destruction during the phase of increased susceptibility to auto antigen, and that its descendents all inherit the rogue ability to manufacture the same auto antibody.[2,13,35] 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 comes close to the somatic mutation theory of cancer. Failures in this mechanism were reported by P. Jacobs, W.M. Court Brown et al, as operative in cases of chronic myeloid leukemia. Chromosome identification techniques showed the emergence of successive clones of abnormal white cells after supression 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 recognised as mutants and destroyed 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 probably in the same way. In autoimmune disease, tissue damage may result in normal tissue from an overactivity of the same system; in tumour growth saturation of, or failure to eliminate all neoplastic cells. Goudham et al have found evidence of lack of normal levels of properdin in people with carcinoma of the skin[3]

Like the tendency to develope cancer, the predisposition to auto immune disease is to some esctent hereditary. The parents of patients with autoimmune thyroiditis show a higher

incidence of thyroid disease than is evident in the population at large.

Goudie[31] reports that auto-immune thyroiditis predisposes to the developement 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 auto-immunity is certainly deserving of further study, but as one progresses the subject becomes more complex and it is doubtful if our knowledge is fare enough advanced to persue this kind of concept further.

However obscure the aetiology of autoimune disease the clinical and pathological features associated with them are well known. The autoimmune disease par excellence is Hashimotos thyroiditis. It is supposed to be a reaction of the R.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.R..[3] Auto-antibodies to thyroglobulin and thyroid cell fractions may be demonstrated in the serum, and occaisionally L.E. cells are found.[12,8,33] Pathologically there is gross fibrosis of the gland, and histology shows a heavy lymphocytic infiltration with 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.

Stuart and Allen[3] have shown that fragmentation of the basement membrane of the thyroid follicle occurs in hyperthyroidism. Many people believe that a transient hyperthyroid state preceeds the developement of auto-immune thyroiditis, others prefer to regard the escape of thyroglobulin as a consequence of some other, possibly infectie, process. Because the R.E.S has never before encountered free thyroglobulin during the stage of impressionability, it forms antibody to it and the disease becomes established.[13,35]

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 auto-immune thyroiditis. This can readily be produced by employing an adjuvant concurrent with the damage to the gland.

Goudie is of the opinion that thyroglobulin leakage occurs normally, and that the disease must be a reflection of some underlying disorder of the R.E.S. Leakage of thyroglobulin has been demonstrated by the use of the radioisotope I^{131} in normal animals and we cannot found 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 thyroglobulin they manufacture, and this may conform to a possible genetical basis for the disease.

The rheumatoid group of auto-immune diseases occupy a place towards the other end of the spectrum. Rheumatoid arthritis presents a puzzling picture. It is now recognised as being a generalised disease with a strong hereditary disposition, due, it is thought, to a single autosomal dominant.(13) Acute rheumatoid arthritis is characterised by low fever, wasting, and a polyarthritis. Anemia, eye disease, which can often be very severe, and skin rashes complete the picture. The disease may be associated with ulcerative colitis, psoriasis, and infections, the most significant being P.P.L.O. organisms and the streptococci.(6,10) The "infective" type of rheumatoid arthritis show a lower incidence of positive sensitised sheep-cell agglutination tests than the auto immune type.

Psychological or infective stresses may serve to "trigger off" an attack, and there is a well known association between this 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 this case appears to be denatured gammaglobulin resulting perhaps from a previous antigen-antibody reaction. The L.E. cell phenomenon is also quite frequently observed.(13,12) Lymphocytes from a normal rheumatoid-arthritic will cause symptoms of the disease in an unaffected recipient.(13)

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

The other member of this group which claims 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 tissues, not the bones and joints. Recent work by J. S. Bana et al.,(37) supported by the work of Weissman and Thomas, has provided a reasonable and very intriguing hypothesis of the possible aetiology of systemic lupus erythematosus, and no apology is made for devoting considerable space to it.

The basis of this hypothesis is that the lysozymes in the cell-cytoplasm in suspension in D.L.E serum are unable to resist the changes in pH subsequent to phagocytosis. As the intracellular pH falls from 7 to 5, these lysozymes disrupt liberating the enzyme desoxyribosenuclease which is then free to attack the cell nucleus. In the nucleus depolymerisation takes place with subsequent death of the cell. The disturbed nucleus is extruded, and subsequently phagocytosed by a polymorph to form the typical L.E. cell.

The cytoplasm of the nucleus of the dead cell act as foreign antigens and give rise to anti nuclear factor and other antibodies, which constitutes the L.E. 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 infective or whatever, has begun the process, it will continue in its absence. Hydralazine induced S.L.E reverses once the aetiological agent has been withdrawn. It is a feature of the "collagen" diseases that hypersensitivity to nucleotide polymers is common.

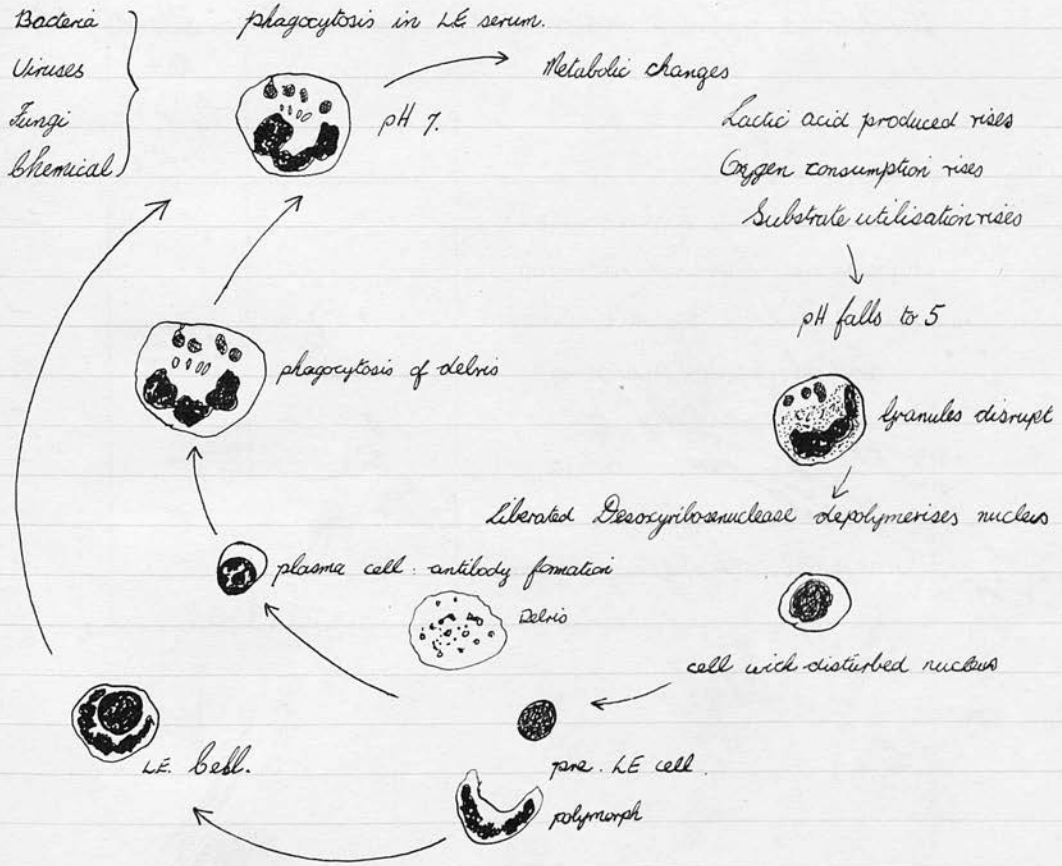
I think it interesting that the best experimental method of demonstrating L.E. cells is not an immunological one, and that cells very like LE cells may be seen in the normal bone marrow smear.(7)

The haemolytic anemias form the most readily studied of all the auto immune diseases, because of the availability of material to study. The auto immune type of haemolytic anemia is generally a secondary or acquired haemolytic anemia. The disease is characterised by an acute destruction of red cells, or "crisis" often following a trivial infection or a vague period of ill health. The serum contains weak, or incomplete antibody which agglutinates both the cells of the patient and those of the normal individual. This antibody is often to one of the rhesus antigens, usually E, 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 sphaerocytic nature. The destruction of the red cells may be intravascular or splenic, but the mechanisms are probably similar to those by which iso-antibodies cause the destruction of incompatible red blood cells. Both cold and warm antibodies are lysed by the complement lysis 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 resection of the spleen. This was a pure case of "hypersplenism" but this trait must be present in all those with autoimmune haemolytic anemias who benefit by splenectomy.(11)

Rheumatic fever has often been held up as an example of auto immune disease, but According to Waksman the best experimental evidence shows that Auto-immunication plays a very minor rôle 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.J. SBARRA. et. al.



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Antihuman globulin serum with	Patients R.B.C.	Normal R.B.C.	
		Rh+	Rh−
Haemolytic Disorders due to		After incubation with Patients Serum	
Hereditary Sphaerocytosis	−	−	−
Autoimmune haemolytic Anemias			
I Without serum antibodies	+	−	−
II With serum antibodies	+	+	+
Isoimmune (erythroblastosis fetalis)	+	+	−
Physical or Chemical agents	±	−	−
Sickle celled anemia	−	−	−
Paroxysmal cold Haemoglobinuria.	+	−	−

many experiments, and conclusive evidence is not available.

Among the latest additions to the already impressive list of auto-immune disease is pernicious anemia.[7,11,16] It was recognised that idiopathic Addisons disease was frequently associated with pernicious anemia. Examination of the gastric mucosa of patients with pernicious anemia revealed heavy lymphocytic infiltration, and this led eventually to the immunological study of the disease. Anti-intrinsic factor antibody and antibodies to parietal cell cytoplasm were found, and also, in many cases, anti thyroid antibodies.[17,22] Using this discovery Gajdusek 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 these phenomena can be explained by supposing a rather general upset in immune tolerance. It has still not been proven, however, that the prescence of antibodies to a tissue will cause disease in that tissue.

Smithers[1] has pointed out that in the malignant lymphomas, or tumours of the R.E.S., many suggestive immunological changes may be demonstrated. In Hodgkins Disease leukopenia, lymphopenia, fever, anemia, and skin changes are all suggestive of a disorder of the immunological processes. Leukocydinis, and anti-red cell antibodies are found frequently, and also anti-nuclear factors occaisionally. There is a strong suspicion that Hodgkins lymphadenoma, lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia and histiocytic leukemia are all separate manifestations of one basic disorder. In each of these diseases auto-immune phenomena have been described. Clones of abnormal tumour cells of the lymphoid series may become autonomous possibly by antigenic deletion and form antibodies to normal lymphoid cells. Evidence supporting this hypothesis is indirect, but multiple infections with poor immune responses, 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.[15,20] An auto immune disease has been suspected in infantile hepatic cirrhosis[15], and in progressive hepatic necrosis which may follow viral hepatitis or other diseases of the liver. The position is not clear in liver disease. Occaisionally anti-liver cell autoantibodies may be demonstrated in obstructive jaundice, toxic jaundice and neoplasia 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

poisoned with carbon-tetrachloride. Despite the rising titres of anti liver cell antibodies after the liver damage no subsequent disease could be attributed to them. The functions of these antibodies may be to protect other cells in the body from toxic products released from the damaged cells, by opsonisation of the harmful fragments. This may account for the occasional L.E. cell seen in these liver diseases.(20)

There are many auto-immune 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 changes in sympathetic opthalmia, ankylosing spondylitis and rheumatoid 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 rather 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 vascularised. The tissue around the graft then becomes heavily infiltrated with lymphocytes around a line of demarcation, and these then invade the graft itself with destruction of the graft cells. The hosts own tissues react with a fibroblastic proliferation and a non-specific inflamation with resulting granulation tissue formation. In about 2 to 4 weeks the homograft "scabs" off and healing of the grafted area takes place. The reaction can be halted by irradiating the grafted 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.(7,12,39)

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 generalised disease, or homologous disease. Secondary disease, runt disease, and wasting disease are all separate aspects of homologous disease.(1)

Secondary disease is caused by "grafting" bone marrow cells from a healdy animal to an irradiated 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 reinfused with isologous bone marrow cells. The severity of secondary disease depends upon the amount of irradiation the host recieves and the "dose" of donor cells grafted.

Runt 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. Burnets esplanation of the cause of the disease is that the new born animals lymphoid tissue is immature and incapeable of forming antibodies, while the mature donor cells are capeable of destroying the hosts tissues unopposed.

Wasting disease occurs when parental haemopoetic cells are injected into irradiated or newborn mice of the F_1 generation. It is similar in all respects to the other diseases descibed. Adrenalectomy 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 too for the surgeon who wants to transplant kidneys, and the physician who wants to give a new bone marrow to the person who has exhausted his own. Burnets theory of the incompetent and competent phases in the development of the lymphoid tissue, gave little hope of ever making a permenant and lasting breach 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 ~~as~~ quantitative respect. It was there, but required a sensitive test to uncover it. J G. Howard and D Michie[42] used as a test the weight of the spleens of animals wid experimentally induced runt 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 10^4 cells. Larger doses than this produced an aggravation of the disease, in fact a type of immunological paralysis analagous 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 mechanisms of homologous disease. The resistance of the adult animal to induced tolerance seems rather to be a function of the amount of lymphoid tissue present than the "qualities" 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 capeable of reacting wid the homograft. Once tolerance has been induced, it will

not be reversed, but a chimeria will have been created. Tolerance is achieved in the adult by reducing the lymphoid tissue with drugs and X ray irradiation.

It seems that I have strayed far from the narrow path of relevance in discussing the homologous diseases, but I hope to arrive back at the original topic by examining the similarities produced by these diseases, and those of an immunological origin. The main feature of homologous disease 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 adrenalectomised rats stimulated or sensitised by injections of Freunds adjuvant, before production of lymphocytes and plasma cells occurs. What is in fact being produced is a "stress", and the subsequent lymphopenia has in the past been attributed to an increase in the secretion of the adrenal cortical hormones. Experimentally it may be shown that steroids do inhibit the metabolism of lymphoid cells, both in vivo and in vitro. But in the adrenalectomised 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 steroid administration, yet the auto-immune disease may be exacerbated by stress of a physiogenic or infectic nature, when the steroid secretion should by all accounts be increased. This apparent paradox is worthy of a better 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 adhesive 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 therefore must be that cell which is able to modify the response of one tissue with respect to another. What gives the lymphocyte this ability, and how is is it controlled? As in so many aspects of immunology 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 responses are discussed,

and the functions of the immune mechanisms of the body are set forth. The criteria for identification of an auto-immune disease are given and the possible mechanisms which may be involved in the production of these diseases are examined. The features of several auto immune diseases are described, with a word about the homologous diseases and the homograft 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 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 irelevant and many of the <u>riaere</u> generalities irritating, because my purpose is not to appear superior, in respect of knowledge or judgement, to my fellows, but to satisfy that part of myself, called curiosity, that is never satisfied. To many others, as to myself, this subject has provided a "look and ye shall find" challenge, in which evidence to quote in support of ones 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 those 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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