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THE PRACTICAL ASPECTS OF AUTO-IMMUNIZATION

By

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In view of the complexity of the auto-immunological problem and the broad front on which research is being conducted I am particularly grateful to our President for having very kindly outlined my theme and I intend to adhere strictly to his suggestions in opening this first session of the "Auto-immunization Committee".

Within the wide range of phenomena covered by the term *pathogenic immunoreactions*, auto-immunoreactions form a group by themselves. I distinguish between those *immediate* reactions which have seric antibodies, *delayed* reactions in which the antibody is contained within the lymphoid cells and *combined* forms in which antibodies are present both in the serum and in the lymphocytes. In these latter forms we have homograft and auto-immunological reactions. It is the auto-immunological reactions to which I shall confine myself.

Auto-immunization is distinguished from other immunological reactions by the fact that there is no introduction of foreign protein, be it heterologous (hetero-immunization) or homologous (iso-immunization). The salient feature of auto-immunization is the production of antibodies capable of reacting with normal or pathological cellular constituents of the same body whereby the tissue acts as antigen. This auto-immune reaction may produce severely pathological conditions.

I shall not dwell on the methods of demonstrating auto-antibodies as this problem will be discussed in detail by Dr.

Torrigiani whom I was privileged to have work under *Dr. Roitt* & *Dr. Doniach* in the Courtauld Institute of Biochemistry of the Middlesex Hospital thanks to Sir Charles Dodds who very kindly acceded to my request. *Dr. Roitt* himself will address us on the auto-antigenic thyroid constituents, having most generously responded to my insistence that he join us.

From the many clinical conditions which may be caused by auto-immune processes I shall mention only a few that may help us in arriving at some general considerations.

It is now widely accepted that acquired haemolytic anaemia is due to auto-immunological mechanism as anti-erythrocytic antibodies have been demonstrated in the majority of cases. Less certain is the role of antibodies in idiopathic thrombocytopenia and leucopenia. It is also interesting to note that antibodies specific for blood clotting factors have recently been demonstrated in some haemorrhagic conditions.

Limiting myself to the practical aspects of *Roitt's* work on the disorders of the thyroid I should like to emphasize the importance of the high thyroglobulin antibody titre found in Hashimoto's disease, as this enables us to differentiate between Hashimoto's disease, cancer of the thyroid and colloid goiter. In the latter two conditions these precipitins are rarely found.

The role of auto-immune mechanisms in renal disease is recently being stressed. Among the most significant data are the finding of gammaglobulin deposits on the glomerular basement membrane as shown by the fluorescent antibody technique, the complement drop during the disease and its accumulation in the presumed locality of the antigen-antibody reaction.

Auto-antibodies have been demonstrated by various techniques and in varying incidence in such diseases as acute demyelinating encephalomyelitis, in rheumatic endocarditis and coronary infarction. They have also been found in cirrhosis of the liver, pancreatitis, ulcerative colitis, Addison's disease, Sjögren's disease, azoospermia, polyneuritis and recently myasthenia gravis and pernicious anaemia. The future may well have further surprises in store for us.

The classical example of systemic disease due to auto-immunization is lupus erythematosus in which a large number of antibodies have been found. From a practical point of view the most important ones are antinuclear antibodies specific for numerous constituents of the nucleus and the majority of workers is agreed that those specific for desoxyribonucleohistone are responsible for the formation of L.E. cells. Other antibodies found in lupus erythematosus are anti-bloodclotting antibodies against factors VII & IX and thromboplastin as well as antibloodcell antibodies reacting with erythrocytes and platelets.

Another systemic disease in which auto-immune reactions appear to play an important role is rheumatoid arthritis in which the antigammaglobulin antibody known as the rheumatoid factor is usually found. The presence of the rheumatoid factor can be used as a diagnostic indication even in very early cases, as it is far less common in osteoarthritis and ankylosing spondylitis.

Having briefly reviewed some of the many conditions in which auto-immune reactions may have a pathogenetic significance (see also *Grabar & Miescher*) and are certainly of diagnostic value, it seems appropriate to mention the *possible mechanisms by which auto-immunization operates in these diseases*.

While there is as yet no general agreement on the basic processes of auto-immunization, it might at this stage seem worthwhile tentatively to suggest a grouping of auto-immune reactions according to the underlying type of auto-immunization. The first group which has been defined as *primary auto-immunization* is characterized by an abnormality in the process of antibody production which leads to auto-antibodies capable of reacting with normal cells or tissues of the body. The typical example of this type of auto-immunization is systemic lupus erythematosus with antinuclear, antibloodclotting and antibloodcell antibodies. Other disorders belonging to this group are acquired haemolytic anaemia due to erythrocyte antibodies, some cases of idiopathic thrombocytopenic purpura with plate-

let antibodies and rheumatoid arthritis with antigammaglobulin antibodies.

As regards the mechanisms of this primary group the hypothesis formulated by Burnet with his concept of forbidden clones is certainly the most fruitful. He postulates the presence of genetically abnormal groups of cells which may be activated into the production of abnormal globulins by various trigger-mechanisms. These globulins then react with those normal cells which are destined to become their antigens. Working with a strain of mice which suffer spontaneously from an auto-immune type of haemolytic anaemia associated with thymic lesions, he concluded that occasional lymphoid stem cells developed a resistance to the normal intrathymic control and that if these have the capacity to react with an antigen present in the thymus, germinal centers and plasma cells may appear in the thymus with the possibility of auto-immune reactions against various body antigens.

The next group—the so-called *secondary auto-immunization*—is usually characterized by the insurgence of auto-antigens in consequence of lesions in various organs. This mechanism may be of two types. In the first it was suggested a *release of previously sequestered or inaccessible antigen*. There are a number of substances which are normally kept in relative isolation from the general circulation such as thyroglobulin, myelin, constituents of the lens of the eye and spermatozoa. When owing to some abnormal process such substances reach the general circulation due to a breakdown of the normal isolating mechanisms, the body treats them as if they were heterologous, they assume an antigenic function, produce highly organ-specific antibodies which react with the antigen and thus produce morbid conditions. Examples of this mechanism are Hashimoto's disease, some types of acute encephalopathy, sympathetic ophthalmia, some cases of azoospermia.

Similar mechanisms have recently been attributed to muscle proteins in myasthenia gravis as also to Castle's intrinsic factor and gastric mucosa in pernicious anaemia.

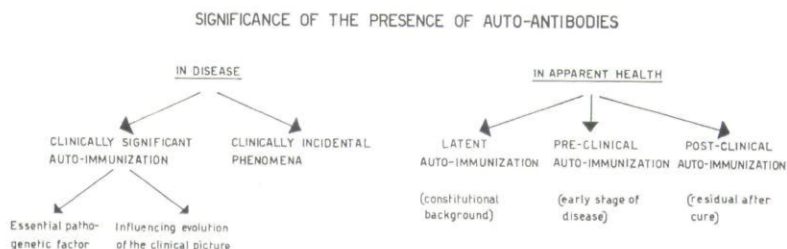
The other type of secondary auto-immunization is that in

which there is an *alteration of cellular constituents* produced by viruses, bacteria, enzymes or chemical action. Constituents of cells subjected to damage may acquire an antigenic function to which the appropriate cells react with the formation of antibodies. This in itself could be regarded as a welcome defense reaction were it not for the fact that these antibodies may cross-react with normal cells. An example of this is the haemolytic anaemia occurring in virus disease. Glomerulonephritis may be due to the combination of a streptococcal antigen particularly M protein with its antibody localized in the basal membrane. The lesions thus produced in turn liberates a new antigen from the basal membrane. In other circumstances we are faced with the intervention of a well defined exogenous factor of known chemical constitution which determines the formation of antibodies by the *haptenic mechanism*. Examples are contact dermatitis and drug induced immunocytopenia.

The most important practical aspect of our problem is the extent to which we can use the presence of auto-antibodies for the definition of auto-immune disease. According to *Witebsky* an auto-immune disease is characterized by the following criteria:

- 1) Direct demonstration of free circulating antibodies that are active at body temperature, or the demonstration, of cell bound antibodies by indirect means.
- 2) Recognition of the specific antigen against which this antibody is directed.
- 3) Production of antibodies against the same antigen in experimental animals.
- 4) Appearance of pathological changes in the corresponding tissue of an actively sensitized animal that are similar or identical to these seen in human disease delayed lesions.
- 5) The successful transfer of the disease by an antibody containing serum or by immunologically stimulated lymphoid cells (*Milgrom & Wietbsky*).

To this it must be said that rare indeed are those diseases which satisfy all these criteria. Only in Hashimoto's disease, encephalomyelitis, acquired haemolytic anaemia and lupus erythematosus do we find the majority of these criteria present. We must therefore distinguish between *auto-immunization* and the *presence* of *auto-antibodies* as the mere presence of the latter may have little or no pathogenetic significance. Auto-antibodies may be classified according to their significance in disease and apparent health as shown in the table.



In *disease* clinically significant antibodies may be essential pathogenetic factor or merely influence the evolution of the clinical picture. In other cases they are purely incidental phenomena. In *apparent health* we may find *latent auto-immunization* as an expression of a constitutional background as has been demonstrated by genetic researches on the families of patients suffering from Hashimoto's disease and rheumatoid arthritis; in other cases we may find *pre-clinical auto-immunization* in the very earliest stages of the disease and finally a *post-clinical auto-immunization* after the disease has subsided. Thus we have to exercise the greatest caution in applying to clinical considerations the presence of auto-antibodies.

Therapeutically we have three lines of approach. One the suppression or reduction of the antigenic focus, as for instance the enucleation of the diseased eye to save the healthy one or subtotal thyroidectomy in case of Hashimoto's disease. Second, diminishing the production of antibodies either by steroid therapy, largely used in the treatment of these diseases, and splenectomy in the case of acquired haemolytic anaemia.

Third, drugs such as butazolidin which diminish inflammatory processes produced by the antigen-antibody reaction.

It is a fascinating thought that our body can live for years in perfect harmony with its own tissues and that then all of a sudden it becomes intollerant and starts viciously to attack and destroy them even to the point of its own destruction in death. We are still at the beginning of a long and arduous road which we hope will eventually lead us to a better understanding of this strange and seemingly senseless behaviour of our body.

REFERENCES

- Burnet, F. M.*: "The clonal selection theory of acquired immunity". Cambridge Univ. Press. 1959.
- Burnet, F. M.*: "Autoimmune Disease—Experimental and Clinical". Proc. Roy. Soc. Med. 55, 619, 1962.
- Doniach, D. & Roitt, I. M.*: "Auto-antibodies in Disease". Ann. Rev. Med. 13, 213, 1962.
- Grabar, P. & Miescher, P.*: "Immunopathology—1st International Symposium". Basel 1958.—B. Schwabe & Co. Basel/Stuttgart 1959.
- Grabar, P. & Miescher, P.*: "Mechanism of Cell and Tissue Damage Produced by Immune Reactions". 2nd International Symposium on Immunopathology. B. Schwabe & Co. Basel, 1962.
- Milgrom, F. & Witebsky, E.*: "Autoantibodies and Autoimmune Diseases". J.A. M.A. 181, 706, 1962.
- Proceedings of the VIIth International Congress of Internal Medicine.* München 5.-8. Sept. 1962.
- Roitt, I. M., Doniach, D., Campbell, P. N. & Hudson, V. R.*: "Auto-antibodies in Hashimoto's Disease (Lymphadenoid Goitre)". Lancet 2, 820, 1956.
- Witebsky, E.*: "Historical Roots of Present Concepts of Immunopathology" in Grabar, P. and Miescher, P.—"Immunopathology" 1st International Symposium, Basel 1958. B. Schwabe & Co. Basel/Stuttgart 1959.

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