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Spontaneous Autoimmune Thyroiditis in Animals as a Model of Human Disease
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In their important review in 1965 Gowans and McGregor [25] established the fact that the ‘immunologically competent cell, which is fully qualified to undertake an immunological response’ [40] is the small lymphocyte. When appropriately stimulated by antigen, small lymphocytes ‘differentiate into large pyroninophilic cells’ which divide ‘to form more lymphocytes of progressively decreasing size’. These divisions transform the uncommitted immunologically competent cell to a committed (activated) cell, which is
able to perform an immunological function. As it is well known, the spectacular
discoveries of Miller [43] and Glick et al. [20] clarified that the primary
lymphoid organs, the thymus and the (avian) bursa of Fabricius and
its functional equivalent in mammals, confer immunological competence to
lymphocytes, which originate from a common stem cell in the bone marrow.
Lymphocytes, which mature in the microenvironment [1 la, 32] and under the
hormonal influence [1,1 la,21,22,37,52] of the thymus develop in the secondary
peripheral lymphoid organs into T cells, which are concerned with the delayed
(cellular) allergic response, whereas those maturing under ‘bursal’ influence,
the B cells, are precursors of the antibody secreting plasma cells [26, 47],
Waksman et al. [54] detected very early (1962) that small lymphocytes after
leaving the thymus (the T cells) reach the peripheral lymphoid tissues, such
as lymph nodes, spleen and gut-associated lymphoid tissue (Peyer’s patches)
via the blood stream and ‘home’ in special areas, namely the paracortical
areas of the lymph nodes, the periarteriolar lymphocyte sheaths of the spleen
and the interfollicular spaces of Peyer’s patches (‘thymus-dependent areas’).
Cooper et al. [11] later found that B cells are located in the follicles and germinal
centers (‘bursa-dependent areas’) of peripheral lymphoid organs. Thus,
the ‘two component concept’ of the lymphoid system [11,23] was established.

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The components of the lymphoid system, the two main lymphocytic populations,
i.e. B and T cells, are interdependent and cooperate extensively with
each other and with other cells as well, e.g. with mononuclear [17] and polynuclear
the lymphoid and phagocytic systems are of decisive importance for the
immune response [8, 44].
Waksman [Introduction to vol. 9, 1965] did not hesitate to state that
the concepts and findings briefly summarized above, ‘have revolutionized
our knowledge’ in this field. The subsequent development, which has been
followed in the volumes of this series, justifies this view.
Lymphocytes are not sessile cells. Medawar [40; cf. also 5, 6, 14, 49]
found ‘immunologically competent cells’ in the blood stream, whilst Gowans
and McGregor [25] described their presence in the thoracic duct lymph and
their circulation and recirculation via the blood stream and the lymphatic
system. Ford states in the present volume that lymphocytes ‘are a nomadic
population which have recently come from the blood, and which will return
to the blood within a period of hours. A large pool of migrating lymphocytes
is continuously been shuffled between the spleen, the lymph nodes and
gut-associated lymphoid tissue. The blood stream serves as a channel for
rapidly redistributing lymphocytes between the scattered lymphoid organs.’
Ford reviews exhaustively the migration of lymphocytes and its role in the immune response. The movements of uncommitted and committed (activated) T and B lymphocytes are thoroughly elucidated. All these cells have ‘their own distinctive migratory properties’. According to Ford ‘the differential migration of these cells depends firstly on selective affinities for the endothelium of small vessels in lymphoid tissue and inflamed tissue and secondly on the ability to segregate after entering lymphoid tissue’. The molecular basis of these processes is a major unsolved problem. The lymphocyte membrane with its array of different surface structures and receptors [50, 51] is one of the decisive factors.

The immediate allergic reaction, the basis of allergic diseases sensu strictior, such as rhinitis, asthma and urticaria, has always been one of the main subjects treated in this series. In vol. 10 (1967), Bloch gave an exhaustive review of the properties of a unique class of antibodies, which is responsible for anaphylactic (immediate) reactivity in several animal species and man. In the Introduction to volumes 11 (1967) and 13 (1969) I tried to depict the impact of the discovery of Teruko and Kimishige Ishizaka, that this antibody, the reagin active in the passive transfer of the immediate reactivity according to Prausnitz and Küstner, belongs to a distinct immunoglobulin class, designated IgE. The simultaneous discovery of a γE myeloma globulin by S. G. O. Johansson [cf. 4] corroborated and extended the findings of Ishizaka and Ishizaka.

In the present volume Ishizaka and Ishizaka contribute a comprehensive review of the ‘Biology of Immunoglobulin E - Molecular Basis of Reaginic Hypersensitivity’. The most important biological property of the unique immunoglobulin IgE is its capability to bind to basophilic granulocytes and mast cells of homologous species (‘homocytotropic antibody’). Ishizaka and Ishizaka treat the physicochemical and immunological properties of IgE exhaustively. The binding of IgE through its Fc portion with the specific receptors on the surface of homologous basophils and mast cells (about 40,000-100,000 per human cell) is thoroughly analyzed. On contact with the specific allergen basophils and mast cells with surface-bound IgE release histamine, SRS-A and eosinotactic factor, which are responsible for clinical signs and symptoms of the immediate allergic reaction. According to Ishizaka and Ishizaka, the prerequisite of the releasing process is ‘probably bridging of cell bound IgE molecules by antigen’. The authors provide ample evidence for this hypothesis, originally proposed and explored by Levine [34a] and recently corroborated by elegant experiments of Massmann et al. [36]. The cell membrane is a ‘fluid mosaic’ [51], the bridging of cell-bound IgE with antigen
(or anti-IgE) induces redistribution of the IgE molecules, ‘cap formation’ is, however, according to the authors, not involved in the process of mediator release. It is not entirely clear how the bridging and redistribution of IgE molecules or ‘some local changes in the membrane structure’ caused by them initiates the enzymatic processes, which result in mediator release [cf. also 42].

The third review in this volume by Tada deals with the ‘Regulation of Reaginic Antibody Formation in Animals’, a field of research to which the author rendered important experimental contributions. The subject of this review tempts me to a remark. The term ‘reagin’ had been coined by Coca [9, 10], in an attempt to differentiate between the ‘true’ antibodies, responsible for the anaphylactic state in guinea pigs and other animals and the factor active in the Prausnitz-Küstner test in humans. According to Coca, anaphylactic antibodies are produced as a consequence of experimental sensitization and are transferable to guinea pigs, whereas reagins are formed without foregoing contact with the antigen and cannot be transferred to guinea pigs. Reagin production is thus peculiar to humans, Coca postulated accordingly that the allergic (‘atopic’) diseases, e. g. hay fever and asthma, are inherited and can only occur in humans. In the first volume of this series (1939), Kalló and Kallós-Deffner [33] refuted Coca’s concept and documented the close relationship between anaphylaxis in guinea pigs (especially when sensitization and challenge are performed through the respiratory route) and allergic rhinitis and asthma in humans. In volume 2 (1949), Wittich [56] reviewed the spontaneous occurrence of allergic diseases in animals, especially ragweed hay fever in dogs.

As Tada stresses, IgE formation in experimental animals can be induced under well-defined and controlled conditions, and can, thus, add considerably to our understanding of the allergic diseases. Tada points out that allergic patients ‘continuously produce reagins upon exposure to minute amounts of environmental allergens, against which the majority of normal people does not produce reagins’. IgE production is ‘persistent and boosterable’. In fact, persistent IgE production in allergic patients is maintained for decades without any renewed contact with the allergen. Cases of food allergy, (e.g. allergy to strawberries) shows this with great clarity. Skin reactivity (wheal and erythema) is according to my extensive experience maintained in such cases for up to 30 years without any contact with the allergen. Minute amounts ingested at that time elicit the signs and symptoms of clinical disease (vomiting, urticaria, angioedema, rhinitis, conjunctivitis, asthma) immediately. Even when these features of allergy cannot be entirely reproduced
in animal experiments, the thorough analysis of experimental results concerning the circumstances which initiate, maintain and finally terminate IgE production in different animal species, is of great importance. The role of species, genetic background, chemical structure and physicochemical state of the antigen, dosage and route of antigen administration and the role of adjuvants (including helminthic infestation and/or helminth extracts) are systematically discussed. In most cases, helper function of T cells is a prerequisite for IgE production. Most important is the analysis of the role of a recently discovered functional class of T cells, the s. c. ‘suppressor T cells’, in terminating IgE production. The general features of T cell suppression of antibody production have been recently reviewed by Gershon [18]. I will also refer to a research report by Marx [38] and a series of publications by Waksman and co-workers [2, 15, 16, 19, 27 a, b, 45]. The suppressor function of T cells is obviously a fundamental immunological activity. Suppressor T cells influence considerably the outcome of antigenic stimulation. Antibody production to foreign antigens and its termination, the development of tolerance, the production of s.c. autoantibodies, some forms of defective antibody synthesis or secretion, are some of the immune processes which are governed by suppressor T cells. Tada discusses their role in IgE production, based on his own important research work. This is a promising novel

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approach, which certainly will be subject of intensive research work in the future.

IgE has possibly some useful role too, which has eluded detection hitherto. Usually, IgE levels remain very low even during bacterial, fungal or virus diseases. As it emerges from the reviews in the present volume no protective effect of IgE in helminthic infestations with high IgE production has been demonstrated. Hill and Quie [29] have recently described a number of cases with repeated severe bacterial and fungal infections, in which defective neutrophil chemotaxis was associated with extremely high plasma IgE levels (2,500-20,000 vs. 30-440 IU/ml for age-matched controls). All of these patients had ‘atopic’ eczema, severe pruritis or urticaria. No explanation for the high IgE values can be given.

Another control mechanism of immune responses is the selective suppressive action by antibody. This important and therapeutically promising area is exhaustively reviewed in the present volume by Fitch. All aspects of the problem are thoroughly discussed. The author stresses that the immunosuppressive effect of anti-idiotypic antibodies ‘which react only with receptors of specifically reactive lymphocytes’ is especially interesting and promising. He clearly exposes all open problems and the review will, hopefully,
provide the basis for further research.
The review by Bigazzi and Rose is entitled ‘Spontaneous Autoimmune Thyroiditis in Animals as a Model of Human Disease’. In a series of pioneer investigations, Witebsky, Rose and their colleagues [48, 53, 55] showed in 1956-1960 that sensitization with thyroglobulin in Freund’s complete adjuvant elicited in rabbits, guinea pigs and dogs the production of antithyroglobulin antibodies of the IgG and IgM class and provoked striking histological changes in the thyroid gland, consisting of disorganization of the thyroid by heavy infiltration of lymphoid and eosinophil cells, closely resembling Hashimoto’s thyroiditis in humans [cf. 12]. Remarkably enough, Rose and Witebsky showed that sensitization of partially thyroidectomized rabbits with their own thyroglobulin led to antibody production and thyroiditis in the remaining part of the gland, a true autologous process. The Buffalo group was thus well prepared when Cole [quoted after Bigazzi and Rose] in 1962 reported on the occurrence of hypothyroid ‘obese’ chickens in a closed flock of white leghorn chickens. The present review summarizes the results of investigations during the last decade concerning the ‘obese’ strain of chickens and other animal species (rats, dogs, monkeys) in which ‘spontaneous autoimmune thyroiditis’ (SAT), which resembles Hashimoto’s thyroiditis in humans, occurs. The authors emphasize the importance of such

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‘naturally’ occurring diseases in contrast to experimentally induced ones, as models of human disease. All features of SAT in the different species are carefully analyzed, compared with each other and with human thyroiditis. A wealth of information is now available but many basic problems remain unsolved. It appears that the prerequisite of the development of SAT in all species is a genetic predisposition, which ‘seems to follow the pattern of polygenic inheritance’. The exact role of antithyroglobulin antibodies and cell-mediated immune responses could not yet been established. The authors consider the possibility that a viral infection of the thyroid in genetically susceptible individuals is the primary event in the development of SAT. Very recently convincing evidence has been presented that the development of another endocrine disease, early-onset insulin-dependent diabetes, has a similar mechanism. In a survey of the pertinent literature, Maugh [39] concludes that this form of diabetes might be an autoimmune disease in genetically predisposed individuals (with high incidence of HL-A 8 and W15 antigens), the pancreatic islet cells of which have been damaged by an early infection with mumps, rubella or possibly other viruses. Maclaren et al. [35] detected by an indirect immunofluorescent technique circulating antibodies belonging to the IgM and IgG class to live tissue-cultured human
insulinoma cells in 34 out of 39 insulin-dependent juvenile diabetic patients (8 positive sera were obtained before insulin replacement therapy was started). The antibodies did not react with porcine insulin. Maclaren et al. [35] state that these ‘findings suggest that autoimmune mechanisms are important in the pathogenesis of most cases of insulin requiring diabetes’. Future work in this field will yield important results for the understanding of these peculiar diseases and s.c. ‘autoimmunity’ in general [7].

The last review in the present volume by Hirschfeld entitled ‘Introduction to a Conceptual Framework in Serology’ concerns the central dogma of immunology, the monospecificity of antibodies. According to Richards et al. [46], it is generally accepted that not only the immunoglobulin population constituting an immune serum is highly specific for the eliciting antigen, but also ‘the individual immunoglobulins constituting this population. This inference underlies arguments concerned with the number of genes needed to provide the observed wide range of antigenic specificity. This inference is still a keystone in much genetic and structural thinking about immunoglobulins.’

In the early days, the founding fathers of immunology, Ehrlich [13] and Landsteiner [34], were concerned with exceptions from the general validity of the dogma. ‘Cross-reactions’ became, according to Heidelberger [28] ‘the microbiologists’ migraine, for they becloud the specificity of agglutinations, hamper their use for unequivocal diagnosis, and perpetuate the hallucination of antigens in common’.

The dogma of monospecificity of antibodies has been challenged by Talmage [52] and from a different point of view by Hirschfeld [30]. The approach of Hirschfeld is purely conceptual. He transformed serologic reactions into verbal codes and analyzed them. In his first paper [30], he stated that a model ‘based on the assumption that antibodies are complex (cross-reacting), permits simpler, more uniform, and less prejudicing interpretations of immunogenetic systems than when antibodies are regarded as simple (specific)’. During the last 10 years he considerably developed this concept. Such an approach is novel in immunology, it is, however, not uncommon in other branches of science [e.g. 31, 41].

The models evolved by Hirschfeld and his conclusions concerning the multispecificity of individual antibodies (‘complex antibodies’) fit very well with the recent experimental results of Richards et al. [46], ‘which support the idea that antibody combining regions contain subsites at which structurally diverse antigenic determinants bind. This concept provides a simple, unifying explanation for a number of seemingly unrelated immunological
phenomena.’ The work of Richards et al. [46] has been based on Talmage’s concepts. It seems to me, however, that Hirschfeld’s ideas had considerable importance at least for the interpretation of the results. The work of Richards et al. [46] signals the beginning of a new era in immunology, which will fulfill the prediction of Heidelberger [28] that ‘visible immune reactions have a chemical basis, so that when cautiously interpreted, the cause of the microbiologists’ migraine may be converted into a valuable tool, even into a kind of biochemical binoculars, affording a clear view of relationships between chemical constitution and immunologic specificity’.

The present volume of Progress in Allergy addresses itself to research workers as well as to clinicians. I hope that the contributions will not only serve as sources of information but also as starting points for discussion and further research work. On behalf of the Editors I express our deepfelt thanks to all contributors and to the publisher, Dr. Thomas Karger.

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