

Pathogenic Importance of Lymphocyte Products

In 1891 Robert Koch concluded that tuberculous infection induced an altered reactivity of infected animals against tubercle bacterial products. It was soon discovered that this reactivity to "tuberculin" was independent of circulating antibodies, and for several decades the exact nature of the immunologically specific "tuberculin type" or "delayed-type" hypersensitivity could not be defined. Some other specific component, different from circulating antibodies, was probably responsible for delayed-type hypersensitivity, and eventually in 1921 Zinsser suggested the clear distinction between two different types of specifically altered immunological reactivity: The immediate type and the delayed type. It was now becoming more probable that delayed-type hypersensitivity was in some way associated with cells, and this was demonstrated in cell migration inhibition experiments by Rich & Lewis about 50 years ago and later confirmed by others. Definite proof that the carrier of this specific reactivity was really the small lymphocyte was given by Landsteiner & Chase (1942).

During the next 30 years the lymphocyte era developed and has probably not yet culminated. But considerable advances in more detailed knowledge about lymphocyte classification, interaction, recirculation, behaviour, morphology, and surface biochemistry have been made. The term "delayed-type hypersensitivity" soon became old-fashioned and was replaced by the term "cell-mediated immunity" or "lymphocyte-mediated immunity", terms that have by now become old-fashioned too. Even, the term "lymphocyte" is now becoming insufficient. If lymphocytes are dealt with in scientific descriptions, a classification label must be included, and classification criteria are needed: On which criteria are lymphocytes classified as B-lymphocytes? How are subclasses of B-lymphocytes defined? What about their place of origin and stage of differentiation? And similarly: How are T-lymphocytes defined? Are they helper-cells, suppressor cells, cytotoxic cells or effector cells? And how is the functional verity behind these terms established? These problems are attracting the interest of thousands of research workers, and initial confusion about definitions and concepts is now fading away, giving room for more clear definitions. The molecular character of the T-lymphocyte receptor which is responsible for the specific, antigen-directed reactivity of the cell is still not completely known. But the mystery of this antibody-independent specific reactivity, which can be followed back in a straight line to Koch is presently becoming gradually disclosed.

When in 1969 Dumonde invented the term lymphokines to signify antigen-released biologically active lymphocyte products, it seemed an appropriate name that covered a need for contemporary terminology. But very soon many biologically active T-lymphocyte products were described with defined roles in the primary and/or secondary immune responses and with regulating, suppressing, helping, chemotactic, cytotoxic, migration inhibitory and other effects. Most often the term lymphokines is now reserved to designate antigen

non-dependent biologically active T-lymphocyte products which have importance in the secondary, antigen-specific T-effector cell-dependent inflammatory immune response. The human leucocyte migration inhibition factor (LIF) is today one of the best defined lymphokines of all.

About 10 years ago the first experiments which utilized antigen-induced LIF activity as indicator of human T-effector lymphocyte-mediated immunity were performed. Since then a vast number of clinical applications of similar techniques have suggested an importance of antigen-dependent T-effector cell activity as pathogenetic factor in infectious diseases, autoimmune diseases, transplantation states, skin diseases and malignant tumours. Some technical improvement in clinical LIF assays has been made, but a real reformation of the test system has awaited immunochemical or biochemical progress. With human LIF both types of research have now led to promising results.

Specific antibody against human LIF can be raised, but can so far only be detected through its very high specific capacity to remove LIF from solutions. However, this achievement has become an excellent tool for checking that a certain migration inhibition capacity of a given solution is really due to LIF and not to some other biological substances. A more promising possibility for developing a clinically useful analysis for LIF is the radioenzymatic LIF assay, which utilizes the enzymatic properties of LIF. In a not too distant future it will probably be possible to detect specific antigen-induced LIF release in the human by a radioenzymatic assay of this type, and quite a lot of suggestive clinical observations obtained with more old-fashioned *in vitro* migration inhibition cultures can be retested and estimated at a more well-defined and informative level. These methods in clinical routine and research can be used for diagnostic purposes in antigen-dependent immunopathogenic states, for monitoring treatment during immunological disorders, for selection of adequate therapy, and for research in pharmacology when attempting to invent or design chemotherapeutic agents that act at selected immunopathogenic steps. The line laid down and presented in Bendtzen's review in the present issue of *Allergy* leads to a future when lymphokine determination may become a routine and an extremely useful tool in clinical work. This clearly opens up great possibilities for new investigations in that large field of medical disorders in which immunological mechanisms are of pathogenic importance.

Gunnar Bendtzen

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.