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Immunity and Concomitant Immunity in Infectious Diseases

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Immunity and Concomitant Immunity in Infectious Diseases

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Immunity and Concomitant Immunity in Infectious Diseases

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Vol. 31

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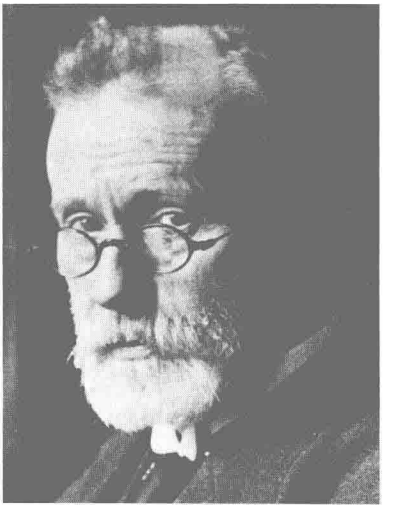
Introduction

Paul Kallós

Clemens von Pirquet
1874–1929



Paul Ehrlich
1854–1915

The present volume is the first of our series entirely devoted to infectious diseases. This gives me the opportunity to remind our readers that the concept of allergy, as brought forward by *Clemens von Pirquet* [6, 8], originated from his meticulous observations of the course of infectious processes, e.g. that of the first vaccination and revaccination against smallpox. He concluded that 'Vaccinated individuals react to the vaccine-lymph, syphilitics to the virus of syphilis, sufferers of tuberculosis to tuberculin, those injected with a foreign serum to that serum, in a different manner, than individuals who had no previous contact with these agents. However, they are far from being insensitive. It can only be stated that their reactivity has been changed. To denote the general concept of specifically changed reactivity I propose the term *allergy*. "Allos" indicates the

deviation from the normal behavior, as in the terms allorhythmia and allotropy.' Moreover, he stated that 'the allergic state is not identical with hypersensitivity, but should unite the great complex of phenomena which we presently denote as "immune reactions." Immunity is then a secondary concept and should be limited to processes which lead to full protection of the organism.' It seems to be important to stress that *von Pirquet* realized that in an organism fully and specifically protected from the pathogenic and toxic effects of a microorganism, the same pathogen is able to elicit immediate wheal and erythema, Arthus- or tuberculin-type inflammatory reactions, processes which are presently denoted 'immunopathologic' and play such an important role, for example, in parasitic diseases that are the main subject of the present volume. *von Pirquet* also realized that anaphylaxis, serum sickness and hay fever are allergic disorders, i.e. due to an acquired specific change of reactivity of the organism against the eliciting agent. He assumed that antibodies, such as precipitins, are causatively involved in the pathomechanism of allergic processes.

von Pirquet's main concern was the fate of the reactive organism. The aim of his great contemporary, *Paul Ehrlich,* was to explore the function of 'the final biological unit: the cell' especially the 'finest chemistry of cell life'. He summarized and conceptualized his achievements and ideas regarding some cellular events connected with infection and immunity in his Nobel lecture [2]. He postulated that 'partial functions of cells' can only be influenced by agents having chemical affinity to the particular cell. Cells are equipped with an array of chemical structures on their surface, denoted 'side chains' or 'receptors'. Nutrients, toxins, pharmacologically active compounds or microorganisms also possess 'definite chemical structures' and are able to interact with cells possessing receptors which are complementary to them, 'fit one another like lock and key.' Antibodies are preformed cell receptors, antigenic agents stimulate the cells bearing specifically corresponding receptors, to generate them in excess and shed them into the circulation. In other words, *Ehrlich* launched the selective theory of antibody formation. Moreover, the receptor theory explained the specific and selective affinities and actions of pathogenic microorganisms, toxins and other biologically active agents. The assumption that pathogenic microorganisms must possess specific receptors, led *Ehrlich* and his co-workers to the discovery of some features of the nature of the interplay between the immunized host and the specific pathogen. Experimental animals (monkeys or mice) infected with a defined strain of trypanosomes developed immunity within 14 days and the parasites disappeared from

their circulation. After a couple of weeks the animals fell ill again and trypanosomes appeared in their blood. The serum of such animals in relapse was able (i) in vitro to agglutinate and kill trypanosomes of the strain used for the original inoculation, and (ii) in vivo to protect naive animals against the pathogenic effect of the original strain. The serum had, however, no effect against the trypanosomes of the 'relapse strain'. *Ehrlich* assumed that a number of trypanosomes of the original strain, which withstood the immune attack were able to change the structure of their receptors and, therefore, the antibodies against the original antigenic structure could no longer affect them, they were 'serum resistant'. He stated that 'it is evident from this that the original strain and the relapse strain are not identical, that they must possess two different functional groups (receptors). We have here, therefore, a typical case of an immunologically evoked disappearance of a receptor, with the formation of an entirely new type of receptor. Whether one wishes to describe this change as a mutation or as a variation is surely of small importance, the main point is that it can be induced... and is inheritable.'

Ehrlich's interest in parasite diseases was evoked by the engagement of his friend *Robert Koch* in the fight against the devastating epidemics, affecting man and domestic animals in Africa. This situation is still prevalent.

I hope that these glimpses into the past show that the genius of *von Pirquet* and *Ehrlich* foreshadowed much of the development in these areas of research. The contributions to the present volume show that progress during the past decade widened our knowledge to an extent nobody could expect, not even the imagination of the great pioneers.

In his contribution to the present volume *Mauël* provides an overview of the 'Effector and escape mechanisms in host-parasite relationships'. The array of humoral and cellular effector mechanisms, such as the protective role of different antibody classes, micro- and macrophages, eosinophils, lymphocytes and their interactions which each other and with the complement system, are highlighted. The esacape mechanisms of parasites, such as antigenic variation, as first demonstrated by *Ehrlich,* and the acquisition of host antigenic determinants or those derived from the normal microbial flora of the host, moreover the recently discovered modulation of the immune response of the host by the invading pathogen, are also discussed. In most instances the first encounter between host and parasite takes place on mucosal surfaces. Therefore, it is of great importance that *Befus* and *Bienenstock* discuss in depth the particular conditions relevant for suscepti-

bility or resistance and the adaptive responses of the host and the parasite at this site. In both reviews the importance of the genetic make up of the host for the outcome of the infection is emphasized. Recent observations regarding the functional heterogeneity of macrophages are of great interest in this respect [cf. 3, 5, 9]. *Befus* and *Bienenstock* stress that protective vaccination against certain parasites is ineffective, perhaps impossible, and that in such cases the best possibilities for symbiosis of host and parasite ought to be determined and established. The life cycle of the parasites outside and within their definitive host is quite complicated. Within the host their development and migration expose different tissues to an array of biologically and immunologically active products. *Mauël* and *Befus* and *Bienenstock* provide in their reviews all pertinent data, which are necessary for the understanding of the interactions of host and parasite.

Jarrett and *Miller* highlight in their contribution the production and activities of IgE in helminth (mainly nematodes and cestodes) infections. They point out that 'helminth infections are unique in stimulating the production of substantial amounts of IgE'. Helminth allergens, probably glycoproteins of low molecular weight, are the most potent polyclonal activators of IgE production. There ist no doubt that helminth-specific IgE antibodies are protective; bound to Fc receptors on eosinophils and macrophages IgE antibodies mediate parasite killing through releasing toxic products from eosinophils and macrophages (e.g. major basic protein of eosinophils and toxic oxygen radicals). Reaction of mast-cell-bound IgE with the corresponding parasite allergen initiates the release of histamine, SRS-A and eosinotactic peptides, which play an important role in worm expulsion. Helminths also produce and release compounds, which are able to degranulate mast cells and basophils independently of IgE. According to *Jarrett* and *Miller* these mast cell activators are at least as potent as 48/80 and their activity results in symptoms which 'mimic' type I allergic reactions. Thus, in helminth-infected subjects specific allergic and pseudoallergic [1] processes occur simultaneously. Further research work concerning the molecular biology of these processes will undoubtedly yield important results for the understanding of the regulation of IgE production and the pathomechanism of type I allergic reactions [cf. 4].

The importance of IgE-dependent cell-mediated destruction of helminths (mainly schistosomes) is further stressed in the contribution by *Capron, Dessaint* and *Haque*. Their meticulous research work has conclusively shown that 'anaphylactic antibody' (IgE, in rats also IgG2a and in mice IgG1) dependent killing of parasites by eosinophils and macrophages

(the role of neutrophils is uncertain) is the main protective mechanism against schistosomula. Schistosomula elicit in men and experimental animals a 'dramatic production of anaphylactic antibodies', which are protective against reinfection. Further development of unaffected schistosomula to adult worms (male and female) can occur and they can live, mate and produce a great number of eggs in the host protected against reinfection, the classical example for 'concomitant immunity' [10]. *Capron* et al. thoroughly discuss the complex immunologic and immunopathologic processes induced by schistosomes. They stress that parasite destruction is mainly effected by IgE bearing eosinophil cells and macrophages in vitro as well as in vivo, whereas lymphocytes do not participate in this process. *Capron* et al. emphasize the general importance of the demonstration of IgE-Fc receptors on the surface of eosinophils and macrophages.

Schistosomiasis is an important model disease, since *Warren* [11] demonstrated 25 years ago that mice infected with the free living form of *Schistosoma mansoni,* the miracidium, develop a disease very similar to that of man. Miracidia penetrate the skin, develop to schistosomula, which migrate through the lungs to the portal and splenic vessels and develop to male and female adult worms. These mate and produce a great number of eggs (a worm pair of *S. mansoni* about 300/day). *Warren* showed that about 50% of the eggs are excreted through the gut, the remaining embryonate. The embryo secretes different antigenic products, among others, enzymes (which enable the eggs to pass through the wall of the gut). These antigens induce a vigorous type IV allergic reactivity resulting in granuloma formation around the eggs. The eggs are then destroyed and the granulomas coalesce to fibrotic foci. This granulomatous process is at the bottom of the hepato- and splenomegaly, leading to portal hypertension and esophageal varices, characteristic for *S. mansoni* infection. Here again, a defence mechanism leads to tissue damage, to an 'immunopathologic' process. The cellular and molecular mechanisms involved have been clarified by *Warren* and recently reviewed by him [11].

The present state of immunological research on African trypanosomes is reviewed in the present volume by *C. L. Diggs*. Tremendous progress has been achieved since the days of *Ehrlich*. His fundamental observation concerning the development of 'serum resistance' of trypanosomes and their evasion of the immune response of the host, due to antigenic variation, has been amply confirmed. The variable antigens (receptors) are, according to *Diggs,* glycoproteins of 45,000–90,000 daltons molecular weight, which are 'represented as a loosely connected surface coat outside

the plasma membrane', it is tempting to say that they are true 'side chains'. The molecular mechanisms of antigenic variation, the cellular requirements of the immune response and the immunopathology of trypanosome diseases are thoroughly discussed by *Diggs*. According to him the achievements of the past decade give hope that 'a major impact on the incidence of these protozoan diseases that currently inflict an enormous burden on humankind' can be made in the not too distant future. *Diggs* outlines the avenues of research, which might possibly lead to the development of a protective vaccine.

The last contribution in the present volume by *S. B. Halstead* deals with the immune enhancement of viral infections. As the author points out ' this review probes the domain of virus replication in vivo. It does so by exploring for the first time the growing literature on the enhancement of viral infection or the enhancement of viral disease by antibody or in immune host systems', The experimental data and clinical observations presented in this review are of very great importance and will certainly 'stimulate discussion and a badly needed critical reevaluation of present day clichés of cellular pathogenesis'.

It was planned to include in this volume a review of malaria immunology, a most important and rapidly growing area of research. Unfortunately, the reviewer Dr. *Anil Jayawardena* of the Yale University, died suddenly of a heart attack at the age of 32 years. He was one of the leading workers in the field of malaria immunology. His untimely death is a great loss.

Finally, I would like to express the deep-felt thanks of the editors to all contributors and to the publisher, Dr. *Thomas Karger,* for their understanding and cooperation.

References

1 Dukor, P.; Kallós, P.; Schlumberger, H. D.; West, G. B.: PAR-Pseudo-allergic reactions. Involvement of drugs and chemicals, vol. 1–3 (Karger, Basel 1980–1982).
2 Ehrlich, P.: On partial functions of the cell (Nobel lecture, delivered in Stockholm, December 11, 1908); in The Collected Papers of Paul Ehrlich, vol. 3, pp. 183–194 (Pergamon Press, London 1960).
3 Forster, O.; Landy, M.: Heterogeneity of mononuclear phagocytes (Academic Press, New York 1981).
4 Ishizaka, K.; Kallós, P.; Waksman, B. H.; de Weck, A. L.: Regulation of the IgE antibody response. Prog. Allergy, vol. 32 (Karger, Basel 1982).
5 Nelson, D. S.: Immunobiology of the macrophage (Academic Press, New York 1976).
6 Pirquet, C. von: Allergie. Münch. med. Wschr. *ii:* 1457–1459 (1906).

7 Pirquet, C. von: Klinische Studien über Vakzination und vakzinale Allergie (Deuticke, Wien 1907).
8 Pirquet, C. von; Schick, B.: Die Serumkrankheit (Deuticke, Wien 1905).
9 Skamene, E.; Kongshavn, P. A. L.; Landy, M.: Genetic control of natural resistance to infection and malignancy (Academic Press, New York 1980).
10 Smithers, S. R.; Terry, R. J.: Naturally acquired resistance to experimental infection of *S. mansoni* in the rhesus monkey *(Macaca mulatta)*. Parasitology *55:* 701–710 (1965).
11 Warren, K. S.: The secret of immunopathogenesis of schistosomiasis. In vivo models. Immunol. Rev. *61:* 189–213 (1982).

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