Von Pirquet, allergy and infectious diseases: a review

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Clemens Freiherr Von Pirquet (Figure 1) was born near Vienna in Hirschstetten, his family seat, in 1874[1]. He took his own life in 1929 at the age of 55. He was successively Professor of Paediatrics at the Johns Hopkins University in Baltimore and in Breslau, before succeeding his teacher Theodor Escherich (of *Escherichia coli* fame) as Director of the Universitäts Kinderklinik and Professor of Paediatrics in Vienna in 1911. His major contributions to science were made mainly before he was 35 years of age when clinical assistant to Escherich in the Kinderklinik in Vienna, that is before 1909.

Von Pirquet entered the field of immunology under the guidance of Rudolf Kraus, who discovered precipitins in immune sera in the University Seratherapy Institute in Vienna. He also collaborated extensively with Bela Schick, who is remembered for his skin test with diphtheria toxin. In the period following the discovery of diphtheria and tetanus antitoxin by Von Behring and Kitasato[2], there was considerable activity in the standardization of horse antisera for therapeutic use. During this time Von Pirquet, together with Max Gruber, Professor of Hygiene at Munich[3], openly questioned Ehrlich's famous side chain theory of antigen-antibody interaction as a result of recalculation of the available toxin-antitoxin neutralization curves. He showed that the curve of neutralization of toxin by antitoxin was not a direct straight line but was asymptotic. To cross swords with Ehrlich, who was then (1903) at the height of his intellectual powers, was extremely brave. However, examination of the data and Von Pirquet's interpretation is completely justified in the light of modern immunological knowledge, and indicated that Ehrlich had chosen to ignore the earlier experiments of Danysz in favour of his own hypothesis of toxin-antitoxin neutralization.

Von Pirquet, however, was no dedicated laboratory worker and preferred to make observations in the clinic. His first large-scale programme together with Bela Schick was a study of serum sickness, in which he made accurate records of the timescale of onset of the reactions, particularly noting the length of the incubation time and accelerated reactions. In these studies he suggested the formation of 'toxic bodies' caused by antigen-antibody interaction. Serum sickness was at that time an extremely topical subject, as the first uses were being described following the introduction of serotherapy for diphtheria and tetanus. However, the role of antibody was not clear due to a failure of clinical manifestations to coincide with the presence of precipitins in the serum. This we now know is due to the presence and action of non-precipitating antibody mainly of the IgE class and to the formation of soluble immune complexes.

The introduction of the term 'allergy' by Von Pirquet in 1906[4] was the direct result of his study of the skin reaction to cowpox vaccination and his interpretation of the reactions observed, based on his earlier studies of serum sickness. It was during an attempt to explain the 'early reaction' that occurs at 24 hours after vaccination that he found the term 'reaction' of immunity inadequate. At that time the term 'hypersensitivity' was applied to general phenomena such as anaphylaxis or local phenomena such as Arthus' phenomenon in which sensitivity could be transferred with serum. Hypersensitivity reactions that could not be transferred with serum, and were thus not antibody-mediated but T-cell mediated, were not recognized. The concept of delayed hypersensitivity as we know it now was not then understood. However, the early reaction after vaccination was believed to be tied up with the immune state of the individual, known since Jenner's time to develop following vaccination. Von Pirquet believed that the exanthem of smallpox was related to the early reaction and both were due to a similar immunological reaction. He felt that immunity and hypersensitivity, although related, contradicted one another and there was a need for a new, more general term, devoid of bias, to denote the change experienced by an organism from its contact with an organic poison, whether live or inanimate. For these general concepts of a change in ability to react he suggested the term 'allergy', meaning a deviation from the original state or normal behaviour of the individual.

Figure 1. Clemens Freiherr Von Pirquet

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The term 'immunity' he felt should be limited to those states in which the introduction of a foreign substance does not result in any clinical reaction.

The question as to whether allergy and immunity in infectious diseases are linked or separate was first raised by Von Pirquet in his study of the early reaction after cowpox vaccination and of the nature of the early exanthem of smallpox[5]. The controversy is still alive and will be returned to later. However, before proceeding it is necessary to introduce Von Pirquet's second major contribution to immunology. This was the cutaneous tuberculin test introduced in 1907[6]. The original test described by Von Pirquet was the application of the tuberculin to a scarified area of skin. During his study of the reaction he made a number of important observations. Firstly, a positive reaction indicated that the individual had had contact with the tubercle bacillus. A negative tuberculin reaction in a healthy small child indicated an absence of tubercular change. In older children and adults a negative reaction ruled out only active tuberculosis. The reaction also disappeared in the final stages of miliary tuberculosis and tuberculous meningitis. Von Pirquet also discovered that the test might be negative for a week in tubercular children who developed measles, which was consistent with the observation that tuberculosis often spread during measles. This is probably the first recorded observation of a virus-induced acquired deficiency of T-cell-mediated immunity.

After his appointment to the chair in Vienna, Von Pirquet contributed little of importance to immunology. He concentrated more on problems of nutrition, mainly as a result of the situation that existed in central Europe during and after the First World War. It might also be said that the problems of infectious diseases and especially tuberculosis could be best tackled at that time by controlling malnutrition.

The term 'allergy' that Von Pirquet found it necessary to invent in 1906 has now taken on a more specific meaning than that originally meant. It covers all those reactions of immunological origin that cause tissue damage and includes T-cell as well as immunoglobulin (IgE, IgG, IgM) mediated reactions. The distinction between allergy and immunity in infectious diseases is clearer than it was in Von Pirquet's time. However, there is considerable overlap and there has been some discussion as to the role of the inflammatory changes associated with the allergic reaction in resistance to infection. This has led to the continuing use of allergic reactions, such as the early reaction to cowpox vaccine and the tuberculin reaction, as markers of specific immunity. Römer in 1908 indicated that, in tuberculosis, hypersensitivity produced destructive effects in the tissues and this was related to the number of organisms present[7]. The hypothesis was therefore put forward that acquired resistance to tuberculosis is effected by the accelerated inflammatory reaction caused by local hypersensitivity. The basis of this view is that inflammation is a known protective mechanism in bacterial infections. Inflammation can wall off and prevent the spread of bacteria. In addition, inflammatory exudates are strongly bactericidal. Hypersensitivity reactions are among the strongest causes of local inflammation. This view was strengthened by the observation that hypersensitivity as shown by the tuberculin reaction parallels immunity so closely that they must represent manifestations of the same phenomenon. Experimentally, guinea-pigs infected with *M. tuberculosis* develop acquired resistance and tuberculin sensitivity in parallel. Neither can be transferred passively with serum, but both can be transferred with lymphoid cell suspensions. Both are manifestations of cell-mediated immunity produced by T-lymphocyte-antigen interaction, resulting in the release of lymphokines and macrophage activation. This mechanism of resistance is important for obligate intracellular organisms such as viruses and facultative intracellular bacteria such as mycobacteria, listeria and brucella, as well as certain fungi.

The role of delayed hypersensitivity in resistance to mycobacterial infection was questioned by Rich[8], enunciated by Mackaness and Blanden[9] and questioned again by Youmans[10]. Rich[8] discussed the fact that a high degree of tuberculin hypersensitivity may be associated either with rapidly progressive tuberculosis or with lesions that are being successfully resisted. Conversely, a low degree of hypersensitivity is compatible either with lesions that are being well resisted or with a devastating one. The dissociation between allergy and tuberculosis in man was also highlighted in the results of the Medical Research Council trial of tuberculosis vaccine[11]. In this study there was no correlation between tuberculin sensitivity and protection from tuberculosis in subjects immunized with BCG vaccine. Moreover, one of the substrains of the vole bacillus, *M. microti*, conferred good protection against tuberculosis and poor levels of post-vaccination tuberculin sensitivity. In experimental studies, Rothschild *et al.*[12] had shown that immunized and hypersensitive guinea-pigs could be desensitized with tuberculin so that they no longer reacted allergically, with accelerated and exaggerated inflammation and necrosis, to the local infection of large amounts of virulent tubercle bacilli or tuberculin. These animals remained as highly resistant to the proliferation and invasion of the bacilli as normal, immunized, hypersensitive controls. These studies were confirmed in a number of centres in subsequent years[8]. The converse experiments were performed by Raffel[13] who injected guinea-pigs with tuberculoprotein and Wax D so that they became highly tuberculin-sensitive but showed no increased resistance to infection. Other studies in both guinea-pigs and rabbits have shown further evidence of dissociation between allergy and resistance to infection in tuberculosis[8].

Despite these demonstrations of a dissociation, there is no doubt that immunity and delayed hypersensitivity develop at the same time in a number of experimental models[9], and experiments on listeria in mice led to the view that immunity in tuberculosis was another manifestation of delayed hypersensitivity in which a stable immunogen was present in killed as well as viable attenuated mycobacteria. It was implied that viable mycobacteria immunized better than dead organisms because of their ability to multiply *in vivo*. This produced more antigen and a more sustained immune response. This view, which held considerable attention, was challenged in a series of studies by Youmans and Youmans[14]. These workers were able to prepare a highly immunogenic fraction from a virulent *M. tuberculosis*. Despite producing resistance to infection, their fraction did not produce an allergic reaction. It would therefore

appear from these studies that immunity and allergy are separate responses to different components of the bacterial cell. Both are mediated by a specific T-lymphocyte response and therefore develop in parallel. However, as different antigens are involved, the responses can be dissociated, although in most cases they continue to run in parallel.

The more recent approach to the question of the dissociation of host resistance and allergy, first studied by Von Pirquet, has been by the development of T-cell clones. As it is recognized that both host resistance and delayed hypersensitivity to certain microorganisms are mediated by T-cells, it was logical to produce antigen-specific T-cell lines which might be cloned to represent the progeny of a single cell selected following limiting dilution of biological active cell population. One of the first studies of this type was that of Lin and Askonas[15], who produced a mouse T-cell line that was cytotoxic for cells infected with influenza virus. These cells transferred delayed hypersensitivity to the influenza virus and also resistance to subsequent infection with the virus. A further study by Kaufman and Hahn[16] on mice infected with *Listeria monocytogenes* demonstrated a clone of T-cells that would transfer delayed hypersensitivity to listerial antigen and protection to live *Listeria monocytogenes*. It therefore appears that both allergy and immunity can be mediated by a single cell population.

However, the question arises as to whether this is a laboratory artefact or representative of the true situation in man. There are now reports of specific T-cell populations transferring delayed hypersensitivity to, for instance, leishmania, that far from enhancing resistance actually exacerbate the experimental disease process[17] by allowing an increase in the number of organisms in the lesions. Thus it would appear that both association and dissociation of resistance and allergy may occur at the single cell level. The important issue is which of these situations plays a major role in the whole individual. Resolution of this question appears no further forward than in Von Pirquet's time. The techniques used for selecting T-cell lines and T-cell clones lean very heavily on the ability of the cells to respond to antigen by proliferation. As this would appear to be related particularly to allergy, the selection process ignores a whole population of T-cells involved in resistance that might not be involved in the allergic response. These cells could well turn out to form the major proportion of the lymphocytes mediating resistance.

References

1 Wagner R. *Clemens Von Pirquet: His life and work.* Baltimore: Johns Hopkins Press, 1968

2 Behring E, Kitasato S. Ueber das Zustandekommen der Diphtherie – Immunität und der Tetanus-Immunität bei Thieren. *Dtsch Med Wochenschr* 1890;**16**:1113; 1145–8

3 Von Pirquet C, Gruber T. Toxin und Antitoxin. *Münch Med Wochenschr* 1903;**50**:1193; 1259

4 Von Pirquet C. Allergie. *Münch Med Wochenschr* 1906;**53**:1457

5 Von Pirquet C. *Klinische studien über Vaccination und vaccinale allergie.* Vienna: Franz Deuticke, 1907

6 Von Pirquet C. Die Allergie probe zur Diagnose der Tuberkulose in Kindesalter. *Wien Med Wochenschr* 1907;**57**;1369–74

7 Römer PH. Spezifische Uberempfindlichkeit und Tuberkulöse immunität. *Beitr Klin Tuberk* 1908;**11**:79–142

8 Rich AR. *The pathogenesis of tuberculosis.* 2nd ed. Oxford: Blackwell Scientific, 1951

9 Mackaness GB, Blanden RV. Cellular immunity. *Prog Allergy* 1967;**11**:89–140

10 Youmans GP. Relation between delayed hypersensitivity and immunity in tuberculosis. *Am Rev Respir Dis* 1975;**111**:109–18

11 Hart PD, Sutherland I, Thomas J. The immunity conferred by effective BCG and role bacillus vaccines in relation to individual variations in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 1967;**48**:201–10

12 Rothschild H, Friedenwald JS, Bernstein C. The relation of allergy to immunity in tuberculosis. *Bull Johns Hopkins Hosp* 1934;**54**:232–76

13 Raffel S. The components of the tubercle bacillus responsible for the delayed type of 'infectious allergy'. *J Infect Dis* 1948;**82**:267–93

14 Youmans GP, Youmans AS. Recent studies in acquired immunity in tuberculosis. *Curr Top Microbiol Immunol* 1969;**48**:129–78

15 Lin YL, Askonas BA. Biological properties of an influenza A virus specific killer T-cell clone. Inhibition of virus replication *in vivo* and induction of delayed hypersensitivity reactions. *J Exp Med* 1981;**154**:225–34

16 Kaufman SHE, Hahn H. Biological functions of T-cell lines with specificity for the intracellular bacterium *Listeria monocytogenes in vitro* and *in vivo*. *J Exp Med* 1982;**155**:1754–64

17 Titus RG, Lima GC, Engers HD, Louis JA. Exacerbation of murine cutaneous leishmaniasis by adoptive transfer of parasite specific helper T-cell populations capable of mediating Leishmania-major specific delayed-type hypersensitivity. *J. Immunol* 1984;**133**: 1594–1600

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