The ALLERGY ARCHIVES

Pioneers and Milestones

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Measles and immunomodulation

rubeola *noun* [Latin *rubolu* redness]
measles *noun* [German *mazer* or *maszern* spots]

Entering the 20th century, much of what was known about measles as a febrile, communicable, exanthematous disease of unknown cause could be credited to 2 historically eminent physicians whose observations were separated by 7 centuries: Abu Bakr Muhammad ibn Zakariya (c.850-923), otherwise known as Rhazes (a name derived from that of his native Persian city of Rayy) and Thomas Sydenham (1624-1689), renowned as the ''Father of English medicine'' and ''the English Hippocrates.''

Rhazes was an alchemist, philosopher, musician, and mathematician, as well as chief physician of the Baghdad Hospital, the era's foremost medical facility, identified with the remarkable Arabian period of creativity and development of science and medicine. In approximately 910, Rhazes (Fig 1) documented the differential diagnoses of smallpox and measles; calling the latter *hasbah* (the Arabic word means ''casting out''; the English equivalent would be ''eruption.'').[1] In 1676, Sydenham (BM Oxford; MD Cambridge), adding his observations and experiences in the 1670 London measles epidemic to his extensive writings on clinical medicine, provided an accurate and detailed description of the symptoms, course, and complications of the disease.[2] Three centuries later, the pioneering immunologist Clemens von Pirquet (Fig 2) added a new dimension to the knowledge base of measles. In 1909, through application of the cutaneous test technique he had developed for the diagnosis and study of tuberculosis, von Pirquet's discovery of the interaction of tuberculin and measles introduced insights into the pathogenetic interface of measles infectivity, immunity, and hypersensitivity.[3]

Clemens von Pirquet (1874-1929) was born into a family of Viennese nobility; studied medicine at Vienna, Königsberg, and Graz (MD 1900); and trained in bacteriology and pediatrics with Karl Escherich at the Children's Hospital and Clinic in Vienna and in immunology with Richard Kraus at the Serotherapeutic Institute. His escalating recognition followed seminal contributions to an emerging new segment of medicine—in particular, coining the word *allergie*, defining the wide interpretation of hypersensitivity,[4] and publishing, with Bela Schick, a classic monograph on serum sickness.[5] In 1911, after a short period in the United States serving in the academic appointment of first head of pediatrics at Johns Hopkins Medical School, Pirquet returned to Vienna and succeeded Escherich as director of the Kinderklinik.

FIG 1. Rhazes (c.850-923) depicted on commemorative postage stamp issued by Iran in 1964.

In the care of patients with infections and contagious diseases, a serendipitous observation provided the genesis of his investigations on tuberculosis and measles:

> The fact that measles has a very peculiar relationship to the tuberculin reaction first occurred to me when a five-year-old boy, who earlier had shown a positive cutaneous reaction, reacted negatively after a hospital infection with measles. I first assumed that it was a miliary tuberculosis which was the cause of the extinguishment of the reactivity, but autopsy revealed lobar pneumonia as the cause of death….Why had the child stopped reacting? I found a clue in the fact that with the onset of measles not only the reactivity to tuberculin, but also a chronic nephritis had disappeared. I had seen the disappearance of the nephritis resulting from measles several times, and so I conjectured that in this case the disappearance of the allergy could also be explained by the measles process. My attention was first drawn to the fact that this absence of reaction appeared not only in individual cases, but rather regularly in all cases, by Preisich (Budapest Medical Association, 1907), who found the cutaneous tuberculin reaction to be negative in all tuberculous measles patients. An examination of my studies that I had made up till then revealed that, of 59 children in the measles ward, 14 had indeed reacted, but that the positive reaction never occurred during the time of the exanthema, but rather only when the children were first examined in a later period…. Since then I have performed the cutaneous tuberculin test on a large number of children in the measles ward from their admission to the 8th or 14th day. Even though the majority of these children constantly remained areactive because of the freedom from tuberculosis, and therefore gave no result in this direction, for that in 24 cases I was able to precisely determine.[3]

Reflecting concurrent systemic loss of the immune-related phenomenon were observations on the exacerbation or reactivation of tuberculosis in patients with measles who had demonstrated pre-existing positive cutaneous tuberculin reactions.

Nineteen years after von Pirquet's tuberculin-measles documentation, a clinical counterpart was recognized in allergic disease. A 1927 publication noted that asthmatic recurrences

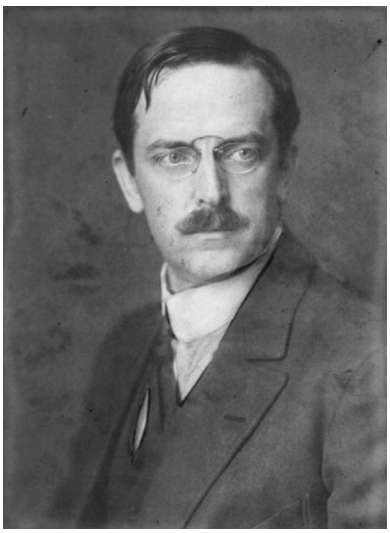

FIG 2. Clemens von Pirquet, MD (1874-1929).

and exacerbations triggered during the measles incubation period subsided coincident with the appearance of the skin eruption and fever. Asthma-free periods remained for the subsequent 2 to 3 months.[6] Verifications and reports of similar findings in other disorders of immediate hypersensitivity followed. Temporary clearing of allergic rhinitis and eczema (atopic dermatitis) during the acute stage of measles, only to recur at some postconvalescent stage, also could be anticipated.

Isolation of the measles virus in 1954 by Enders and associates enabled their production of an attenuated live vaccine 6 years later. The resultant availability of a live immunizing agent that effected subclinical production of immune responses identical to those of naturally acquired measles provided an additional resource for the study of measles suppression of delayed hypersensitivity. Identical capacities of naturally acquired measles and attenuated measles virus vaccine to interfere with recipients' cutaneous expressions of other instances of delayed hypersensitivity without evident effects on humoral antibodies were subsequently demonstrated.

Suppression of delayed skin test responses to candida and vaccinia, diphtheria and streptococcal antigens (Schick and Dick tests), rhus (poison ivy), and 2-4 dinitrochlorobenzene contact allergens were identified. Counterpart phenomena of the *in vitro* capacity of lymphocyte blastogenesis on stimulation by tuberculin and candida were equally impaired in measles virus–affected patients. Underscoring selective measles immune-suppressed, cell-mediated reactivity was the lack of decrease in pre-existing diphtheria toxoid and poliomyelitis antibody titers, quantitative measurements of serum gamma globulins, and inhibition of induced, cutaneous, wheal-and-flare, immediate hypersensitivity reactions. That suppression of cutaneous and correlated *in vitro* cell–mediated delayed hypersensitivity was dependent on measles infectivity and not virus antigen *per se* was evident in the lack of demonstrable effect in recipients of inactivated killed virus vaccine.[7]

Although extended investigation did not uncover an explanation for the exact mechanism, the relative lymphocytopenia characteristic of measles offered a clue. Variable failure of lymphocytes recovered from patients with measles to mount an *in vitro* proliferative response to PHA mitogen[8] suggested toxic action on infected cells. However speculative the mechanism, less than normal T-cell counts and pertinent investigative leads pointed to direct viral attack on and lysis of lymphocytes.[9]

Lymphocytopenia has also been found to occur in other viral diseases: poliomyelitis, influenza, enterovirus and rhinovirus infections, and yellow fever. However, measles antigen remained unique in its alteration of the immune equation. Attempted immunization with killed vaccine not only failed to generate hemagglutination inhibition antibody and protection against infection in the nonimmune but rather brought about an unusual state of altered reactivity.

In the 1960s, children who had previously received killed inactivated vaccine on exposure to measles had an atypical illness. Not recognizable as measles, its symptoms were characterized by fever, pneumonia, variable peripheral edema, and a skin eruption that differed in site of onset on the feet, cephalad progression, predominate distribution on the lower extremities and flexural creases, and the papular, petechial, vesicular, and urticarial character of the lesions. Extending investigation of this manifestation and its pathogenesis, Fulginiti and Arthur[10] demonstrated delayed, indurated, local reactions to intracutaneous injections of corresponding vaccine only in those who had received killed virus vaccine typical of a delayed hypersensitivity test reaction. This implication of the causative mechanism for atypical measles added another instance of measles-related immunomodulation some 60 years after that documented by von Pirquet.

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Disclosure of potential conflict of interest: S. G. Cohen has declared that he has no conflict of interest.

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