lished. All sources of infection, such as infected tonsils and teeth, should be removed, nasal deformities interfering with proper breathing (deviated septum) corrected. In a great many instances the building up of the resistance will be accomplished by sufficient rest for the child, by proper, well balanced diet including rich milk and cod liver oil in any form. If such a program is carefully carried out, I believe it will aid many children in arresting the mild lymph nodes disease that they already have. This, in turn, with the proper advice and education they receive from the family physician will prevent severe forms of adult tuberculosis from developing.

It has been said that “for tuberculosis we prescribe not medicine, but a mode of life.” By realizing that, our task will be greatly facilitated.

Glenn Dale Sanatorium.

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Allergy in Tuberculosis

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When contact with a foreign protein (pollen, vegetable, animal or bacterial) that has penetrated the tissues is established, the first, ordinary or normergic response of the body varies from a mild reaction to a severe inflammation, depending upon the inherent toxicity of the agent and upon the quantity. After an incubation period, the body is then sensitized to the foreign substance, and upon repeated exposure to it the inflammatory response differs from the original reaction in that the onset is acute, the course more violent, and the resolution of the process slower. Hyperergic reactions of this sort, analogous in many respects to conditioned reflexes, occur not only in the clinical allergies but also in other forms of anaphylaxis, in idiosyncrasy, and in immunity. Van Pirquet in discussing the phenomena which he had included under “allergy,” said as follows: “We rightly use the word ‘allergy’ from ergia, reaction, and allos, altered, to mean a changed reactivity as a clinical conception without being prejudiced by the bacteriological, pathological or biological findings.”

This clinical conception, however, was of sufficient importance to give a new interpretation to nearly all the phenomena observed, whether bacteriological, pathological, biochemical or immunological in tuberculosis, and especially in diseases in which hypersensitivity plays a part.

Pottenger in 1929 wrote as follows: “Without the consideration of allergy we can no more understand the pathological changes and varied clinical manifestations in tuberculosis than we can understand its etiology without considering the tubercle bacillus.”

Koch's description of the cutaneous reaction to reinfection expresses the greater part of what is known today concerning the relation of sensitization to immunity in tuberculosis. In a guinea pig infected with tuberculosis for the first time by injection into the skin, the cutaneous lesion appears slowly and persists until death, but in a previously infected animal an intense inflammatory reaction associated with superficial necrosis produces an ulcer that quickly heals without infection of the neighboring lymph nodes.

It has been well established, that allergic reactions are influenced by the number and size of the sensitizing and shocking doses and by the time intervals. They vary from functional, vascular responses and hypertonus or spasm of smooth muscle to the severe, necrotizing inflammation characterizing the Arthus phenomenon. Under certain circumstances specific granulomatous lesions result. Although it is possible that all the cells in the body may be sensitized, allergic reactions are ordinarily exhibited by the arterial system, connective and lymphoid tissues, and synovial, ectodermal and entodermal membranes, whereas the parenchymatous tissues are usually spared.

According to Rossle the allergic reaction may consist entirely of a focal hyperergic reaction localizing the antigenic poison as in the Arthus phenomenon; and this organ or tissue disease prevents a blood disease. If, however, the hypersensitive state is mild or the shocking dose is extremely great, regardless of local blockage by hyperergic inflamm-
mation, some of the antigen spills over into the circulation, the protection of the individual is taken up by the spleen, liver and other related protective mechanisms. If still more antigen enters the blood stream, the physiological anergy of the remaining endothelium changes to hyperergy, and by the arrest of living or dead poison on the intima, various vascular granulomata result. If this last defense is finally broken through, the antigen permeates the tissues and produces different types of inflammation depending upon the type and degree of the allergy. The successful production of endocarditis, arthritis, and myocarditis resembling the lesions of rheumatism by repeated and attenuated doses of living or dead antigens may be explained on this basis.

Rossle directly observed the changes of normergic and allergic inflammation in frog mesentery preparations. Frogs previously sensitized to swine serum, upon reapplication of this foreign protein reacted with a prompt stasis of the blood much greater in extent than in the control animals, and at the margins of the poisoned area there was a reversal of capillary blood flow. In addition there was a much more intensive accumulation of fluid and leucocytes in the sensitized animals, a greater tendency to hemorrhage and finally a greater delay in the resolution of the process.

We have been able to observe reversible histological changes to antigens such as ragweed and house dust in experimentally produced wheals in allergic individuals. These inflammatory reactions were similar to those seen in the well known clinical allergies, hay fever, asthma, etc., all characterized by considerable edema and infiltration with eosinophiles, plasma cells and other wandering cells. Involved mucous membranes also show evidence of hypertrophy of smooth muscle and active secretion of mucus. Kline and Young observed this type of inflammation in nasal and sinus mucous membrane in twenty-nine cases. Similar observations were made by Finck, Hansel, Weille, and Coates and Ersner and are amazingly similar in spite of varying antigens. Similarly, post-mortem descriptions of tissue changes in bronchial asthma, similar to the above, appear in the literature by Huber and Koessler, Kountz and Alexander, and Steinberg and Figley.

In certain diseases such as tuberculosis, rheumatic fever, and syphilis, the allergic inflammatory tissue changes may be not only reversible as in the positive tuberculin skin reaction and slowly resolving exudative pneumonia in tuberculosis, but also, of the more persistent granulomatous type as typified by the early tubercle, Aschoff body, and early gumma, produced by specific substances after the body has been properly sensitized.

For von Pirquet, hypersensitivity meant liability to symptoms, while "insensibility," abolished reactivity meant immunity from symptoms. "It has been shown," he writes, "that the symptoms of infectious diseases are not entirely due to the action of microorganisms per se, but that, in any disease, the organism itself takes an active part in the production of most symptoms by an interaction of products of its own with products derived from the infecting agent. The products by which the organism participates in the reaction are the so-called antibodies." In discussing the special application of his concept to tuberculosis, he points out that the simple antibody antigen explanation does not seem "to cover all the types of tuberculin immunity. The reason seems to be that beside the one antibody which we considered until now, other antibodies are also involved in the process."

More recent investigative work has certainly proven the tubercule bacillus to be a highly complex organism from the chemical viewpoint; and it is interesting to point out that von Pirquet was not far off when he stated that more than one antibody might play a part in the altered reactivity of tuberculosis, as the following extract from a paper by Smithburn and Sabin proved: "The lipoid portion of the organisms, notably a phosphatide constituent, possesses the capacity of producing tuberculous tissue; that is, epitheloid cells and giant cells. The so-called waxes cause a proliferation of fibroblasts. The acetone soluble fat induces proliferation of all connective tissue cells and of blood and causes hemorrhage. The polysaccharide is chemiotactic for and toxic to leucocytes. The protein is probably responsible for fever and, in addition, causes a proliferation of plasma cells."

The views of Smithburn and Sabin offer a marked contrast to the less certain atti-
tude of von Pirquet. Although the problem is still very complex, their statements are based not on wish fulfillments, but on very carefully executed experiments with purified fractions of large amounts of tubercle cultures and their results have checked on repeated tests. It appears, therefore, too narrow a conception, if one limits the term allergy to just one part of the altered state of reactivity which follows tuberculous infection.

Hypersensitivity to the tuberculo-protein is not the entire picture of allergy; the change toward immunity must be included, and to limit the use of the word “allergy” to hypersensitivity is to discount other altered reactions of like clinical importance.

I share the view of Cummins in that “allergy” in tuberculosis is an expression of altered reactivity in the human or animal organism resulting from infection; a new state results in which some individuals respond to a given amount of infection by becoming extremely sensitive to tuberculin and yet may show no resistance if the infection develops into disease (e.g., many of the negro race), while others, perhaps less hypersensitive, may be highly resistant (e.g., the Hebrew race). It seems, therefore, that one of the important functions of “acquired immunity” is to protect the infected individual from the effects of hypersensitivity.

For purposes of clarity it appears that altered reactivity in humans in relation to the tubercle bacillus and its products may be divided into three stages as follows:

Stages of tuberculosis (in terms of altered reactivity to the tubercle bacillus and its products): Normergic (neutral); 2. hyperergic (hypersensitivity): (a) mild, (b) marked; 3. Immunity: (a) negative, (b) positive.

Let us consider this classification from the practical viewpoint.

Normergic

This stage is seen early after the first infection. It is noted in experimental animals during a brief period following the inoculation, by retention of health, normal gain in weight and an absence of tuberculin sensitivity. It is observed in man in the period which elapses between the earliest contact of a newly born infant with a tuberculous sensitivity; a period which may vary from weeks to years, depending upon the virulence, quantity and frequency of infection, and possibly upon “natural immunity.” In von Pirquet’s sense, it is the “incubation period,” the period of antibody formation. Its expression in the tissues is seen in the “primary lung focus” and in the early glandular foci, small localized lesions surrounded by healthy tissue without any sign of surrounding reaction and usually healing by peripheral fibrosis and central calcification. During this stage, the tubercle bacillus on reaching the body tissue of fluids, is no more destructive than a dust particle; reacted upon by the same phagocytes and carried along the same lymphatic route as a dust particle; and finally disposed of in the same situations or filtered out in the same collections of lymphatic drainage, by which dust, like the tubercle bacillus, travels to the glands. There is this difference between the dust particle and the tubercle bacillus. The dust particle cannot multiply, although it may produce local irritative changes. The tubercle bacillus, highly resistant to enzymes, multiplies until its increase is either limited by cellular barriers or destroyed by focal bactericidal elements. At this point, the stage of normergy or neutrality passes on, first to the stage of “mild hyperergy” and later either to that of “marked hyperergy” or possibly under favorable conditions, to relative “immunity.”

Hyperergic

Mild Hyperergy—The stage of mild hyperergy is that in which most of us exist. It is brought into existence by the escape from the original focus of infection into contact with our body tissues, not necessarily with the tubercle bacillus alone but with its chemical end products, which changed by the antibodies now forming, have the power to change our entire constitutional “being” with a newly acquired reactivity. This new state is quite compatible with normal health and development and its presence is only brought to light by the tuberculin test. All that this proves at present is that infection has taken place.

Von Pirquet wrote: “if we make tests on people of different ages, we find progressively with the increase in age a growing percentage of clinically healthy people who show very slight reactivity. We might assume that in these people we are confronted by a period of lessened reactivity several years after an
acute stage. "Mild hyperergy" is a state which, following reinfection, either intrinsic or extrinsic, will be followed by a marked local and systemic reaction; in other words "marked hyperergy" to tubercle bacilli and their products.

Marked Hyperergy—Krause\(^{19}\) explains the symptoms of tuberculosis as follows: "Human beings pass perfectly well as long as they hold their tuberculous infection asymptomatic. But they are allergic and any discharge of sufficient focal material to a new place will render them immediately ill because of the allergic reaction that ensues promptly." Wright\(^{20}\) apparently had similar thoughts twenty years earlier when he advanced his theory of "autoinoculations." He said: "Intoxication phenomena and immunizing responses, exactly similar to those which supervene upon the inoculation of bacterial vaccins, must occur whenever bacterial products or, as the case may be, bacteria, escape from localized foci of bacterial infection and pass into the circulation." This seems to be exactly what occurs in tuberculous disease. The symptoms which follow a large dose of tuberculin in a healthy but infected person, a person in the stage of "mild hyperergy," are exactly those which occur daily in the subject of active tuberculosis as the result of autoinoculations from his active foci, malaise, headache, lassitude, and fever; Koch himself described these symptoms experienced by himself after having taken an excessive dose of old tuberculin subcutaneously. This differentiates between "mild" and "marked" hyperergy. Koch, an infected but healthy person, was only proved to be "mildly" hyperergic to the products of tubercle bacilli when these were artificially introduced into his circulation from the outside. His own foci of infection were, for the purpose of autoinoculation, extinct. But, in the "markedly hyperergic" stage the infective foci in the body are not extinct but active; or, when absolute rest has been imposed, in a quiescent state easily passing back into an active state if undue bodily exertion is unwisely attempted.

Robert Koch says: "Individual cases of the disease, have often shown that a person is not at all times an equally favourable subject for the development of parasites, for it not infrequently happens that tuberculous foci which had reacted to a fair size, contract, cicatrize and heal up." This is so often seen to occur either with or without therapy, and it implies a changed reaction present in the area of the tuberculous foci, and adaptation of the related tissues and fluids by which they are permeated to the focus and its contents so that the latter does not escape or is rendered harmless by being neutralized in some way. This altered state is to be considered as a state of immunity to the tubercle bacillus and its products and leads us to a consideration of the factors which seem to operate its activity; since it is this phase that treatment is aimed at, so that it may operate at maximum speed.

Immunity

Negative Immunity—Since "negative" immunity or "anergy" is a terminal state and occurs when treatment usually fails, there is little point in discussing it.

Positive Immunity—As has been suggested elsewhere in this paper, positive immunity depends on the diminution or complete neutralization of the effects of autoinoculations. In the spontaneous cure of symptoms, this effect must be gained by surrounding and isolating tuberculous foci and rendering these areas harmless by scar tissue about them; or through neutralization by chemical or physical means or by absorption of toxic products. There is experimental evidence that both types of defense are utilized in tuberculo-immunity. The experiments which show that tuberculous foci can be rendered innocuous, are presented to the eye through microscopic examination of certain types of tuberculous foci in which it is visibly apparent that the surrounding tissues are free from inflammatory reaction.

Cummins and Weatherell\(^{21}\) have shown by their experiments with intravenous infection of rabbits with large doses of human tubercle bacilli, that "neutralization of toxins" results. These investigators showed that there was a "danger" period corresponding to the development of allergic hypersensitivity, which resulted in a number of deaths in the third and fourth week after infection and during which all infected animals were very ill. In those dying, the lungs showed marked inflammatory reaction about the numerous bacterial foci resulting from intravenous injection.
the animals regaining their health, examination of their lungs revealed almost entirely healed areas without scar tissue formation. The earlier inflammation had been overcome and the exudate absorbed even though the lung lesions were still active.

From the evidence presented it seems that, in this disease, and in many others in which chronic bacterial foci and resulting hypersensitivity play a part, the body is faced with the problem in which efforts at spontaneous cure tend to defeat themselves. In the one case, the lysis of the tubercle bacilli destroys harmful germs but liberates harmful toxins. In the other case, the cicatrization of their lungs revealed almost entirely healed areas without scar tissue formation.

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3 Pottenger, F. M.: Tubercle, 10: 409, 1929.

1941 Diseases of the Chest

Summary

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DISEASES OF THE CHEST

May

17 Smithburn, K. C. and Sabin, P. R.: Jour. Exper.

PROGRAM
Seventh Annual Meeting
American College of Chest Physicians

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