strips off one of the long longitudinal strands from the inner side of the peeling, and treats this with ferric chloride, the chains are found to be made up of small masses of a garnet-colored substance, each contained within a cell membrane. The garnet-colored bodies are evidently the contents of the cells (Fig. 3). If examined in a fresh state, unaffected by chemical agents, these cells are found to be chains or threads of homogeneous bodies united end to end, soft enough to be influenced by pressure upon the cover glass, which causes them to burst and exude a gelatinous, colorless mass. The chains run in pairs, surrounding the fibrovascular bundles. In the botanical literature, put at our disposal by Professor W. Trelease, of the Missouri Botanical Garden, were found but few references bearing directly upon the subject. In Engler and Prantl²⁵

FIG. 3.—A small portion of a banana treated with a 10 per cent. aqueous solution of ferric chloride (magnified 70 diameters), showing double chains of milk-tube cells accompanying the fibrovascular bundles, with parenchyma cells intervening.

reference is found to the milk tubes in the *Musa*, which consist of cylindrical rows, one above the other, of cells rich in tannin. De Bary²⁶ refers to jointed milk tubes (*gegliederte Milchröhren*) produced by end to end fusion of cells, and says: "In the stem, as well as in the fruit, the vascular bundles are accompanied by milk tubes two to six in number, symmetrically arranged and separated from them by one or two layers of parenchyma cells. . . . These milk tubes consist of a row of vertical cylindrical cells, one above the other, four times as long as they are wide, and through a round wide opening at each end are converted into a continuous tube. They contain large homogeneous, highly refractive resin balls or masses, suspended in a fluid very rich in tannin."

These resin balls, then, the contents of the cells, suspended in a fluid rich in tannin, are affected by the secretions of the stomach

²⁵ *Die Natürlichen Pflanzenfamilien*, 1859, II, 6.

²⁶ *Vergleichende Anatomie bei Phanerogamen und Farnen*, 1877, pp. 153, 160, 451.

and intestine in a manner similar to the action of the ferric chloride, hardening the resin and producing an insoluble tannate. The cell wall is digested or destroyed, and the hard resin-tannin-containing mass is liberated as a grain of sand. The extreme hardness of the grains found in the feces is due evidently to the prolonged influence of the secretions and salts in the intestinal canal, and the color to a tannate formed, influenced perhaps to some extent by other coloring matters in the intestines. We were unable to give the same hardness to the sand produced artificially outside of the body through treating it with hydrochloric acid and pepsin, saliva, pancreatin, ferric chloride, or by mixing it with the feces, etc., though nearly all of these agents hardened the grains to a certain degree and gave to them the typical color. Thus far, we have been unable to find other fruits or vegetables which give rise to similar bodies.

That intestinal sand may be produced through the ingestion of the banana has been proved by us beyond a doubt; that the descriptions of the sand reported in the literature by some authors seem identical with ours is certain; that many of these were due to the ingestion of the banana, or some other fruit or vegetable having like structure, seems most probable.

GENERAL AND SPECIFIC RESISTANCE TO TUBERCULOUS INFECTION.

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BEFORE discussing general and specific resistance to tuberculous infection, I wish to refer briefly to infection in general. Omitting much that would perhaps be relevant to a fuller elucidation of the subject, I may state the accepted fact that a bacterial invasion of a living organism can occur only when the related bacterium finds conditions favorable to their life and multiplication within its tissues, and that the action of their toxic products depends upon a receptivity for them by the component tissue cells. The primary effect and the course of such an infection may be influenced or modified by the bacteria themselves: first by the number of living units which have gained entrance, and, second, by their life energy and their adaptation or virulence for the particular species of animal. The character and function of the tissue in which the growth and multiplication of the bacterium takes place, and in any case their biochemical properties have a determining influence.

When an infection has actually occurred, one of three things can happen: (1) The bacterium may be destroyed; (2) they may

continue alive, but are prevented from growing and multiplying; and (3) they may grow and multiply and in due course of time produce their characteristic effects. In such a case a small number of living bacteria would be of but temporary influence, the evolution of the disease could for a time be slower, but so long as growth and multiplication is possible, the disadvantage of a small number would in time be overcome when new generations have formed, and these would likewise be free from the effect of a check in vitality which might have occurred to the bacteria which were primarily concerned in the infection.

Virulence is so closely associated with growth and multiplication and the latter with the nutritive soil, that many observers consider growth-energy and virulence to be identical. That the composition of the soil is of importance is well known from experience in the artificial cultivation of pathogenic bacteria, although this permits of a materially greater variation than is likely to be present in the tissues of the same species. When we nevertheless observe it in the latter, it is because we deal with a living soil, which is subject to influences of a biochemical nature; and in addition to *substance*, we are obliged to take into consideration *vital functions* of a very complex nature. These functions are of cellular origin and can be general or special; in their general aspect they are intimately related to cell nutrition, and in their totality and integrity they constitute the normal manifestations of life.

Some of them are regulative and thereby protective in maintaining a properly adjusted balance. Minor disturbances, and especially such as are frequently repeated, are adjusted automatically and rapidly enough for the individual to remain unconscious of their occurrence. Others, of a severer degree, and especially such as are unusual or entirely new, manifest themselves in what we call disease, and then the restoration of the balance may occur more slowly or it may fail. This depends upon the nature and degree as well as upon the duration of the disturbing factors, and in infectious diseases latent cell functions may become active, or apparently new functions may develop to aid in the restoration of a normal equilibrium.

These general principles apply to all disturbances of normal life conditions, and those which are produced by pathogenic bacteria conform to the same general laws. The fact that our understanding of these laws is often only fragmentary and, therefore, greatly limited, does not justify their denial, even though we see apparent contradictions. Many such have in the past confronted human inquiry on other subjects, and often in simpler propositions than in those pertaining to the study of the phenomena of health and of disease; and some of them have finally found their elucidation upon these same primitive principles. All such studies required in the first place the formulating of theories, and for the origin of tuberculosis the theory of its direct inheritance or of a

special inherited predisposition is but natural for the time in which it was evolved. When theories, however, do not find support in observed facts, or when new facts are discovered with which they cannot be brought into harmony, then they require reconsideration, which may necessitate modifications or their entire abandonment.

Such reconsiderations have engaged the attention of many able students of tuberculosis, especially since the actual demonstration of the strictly infectious nature of the disease as a new fact, and the study of immunity since then has added other facts which I believe to be out of harmony with some of our former views and with accurate clinical observations.

The latter have shown that good preëxisting health and a perfect family history by no means protect against the acquirement of tuberculosis or even modify its course favorably, and the evidence is growing stronger that impairment of health before the outbreak of the disease depends frequently upon a tuberculous infection which, by its hidden localization or by its earlier insidious progress, was overlooked.

The enormous tuberculosis mortality among primitive peoples, when once they are exposed to infection, in whom we see likewise the least resistance in its course, is also significant and supports the view that individuals and races are primarily non-resistant and that subsequent generations develop previously latent or new protective functions which become efficient in proportion to the frequency with which they have been exercised in the ascendants. For the lack of resistance in such primitive peoples to tuberculosis I need but cite the observations collected by Hirsch¹ in regard to negro and other races in their native countries, and those which have been made on the negro and Indian population in the United States.² The interested student will find additional data in the publication by Reihmayr,³ not only for comparison of prevalence and mortality in aboriginal races before and after the advent of tuberculosis among them, but also evidence that the frequency and fatality of the disease decreases in civilized races, accordingly as they have had to contend with the disease for longer or shorter periods of time. Reihmayr's data are supported by similar studies by Marengos,⁴ Fishberg,⁵ and others upon the Jewish race; and although the presumed resistance of the latter is no doubt often overestimated and may be variously modified and lowered, the correctness of the claim of their greater resistance, becomes apparent when their mortality and morbidity from tuberculosis is compared with that of peoples who have more recently come under the influence of the disease and who are otherwise living under similar or even better conditions.

¹ Historisch-Geographische Pathologie, Stuttgart, 1886, iii, 156.

² Martin, Trans. Nat. Tub. Assoc., Washington, 1906, p. 91; Jones, Ibid., p. 97; Harris, Jour. Amer. Med. Assoc., 1903, xli, 834; Adams, Medical Record, 1907, xxxiii, 833.

³ Die Ehe Tuberkulöser und ihre Folgen, 1894, 35.

⁴ Grèce médicale, October, 1901.

⁵ Amer. Med., 1901, ii, 695.

A recent study by Woods Hutchinson⁶ shows, among certain tribes of American Indians, a tuberculosis mortality of from two-thirds to three-fourths of all deaths, and this author, like Effertz⁷ and many others, calls attention to the rapidly fatal course of the disease among the Indians from which previous robust health and physical vigor was unable to protect.

The observations of Johnston⁸ of a difference in morbidity of 60 to 65 per cent. as between European and native troops in the British army in India, and the records of 290 deaths from tuberculosis per 1000 hospital admissions in the Egyptian army recruited from natives, as shown by Captain Cummins⁹ cannot be well explained upon any other theory than that Europeans are possessed of a certain degree of racial resistance. On the other hand we have all observed more or less numerous instances of long continued exposure with apparent escape from infection or of a favorable, or an extremely chronic course of the disease, in individuals whose physical and general condition was anything but indicative of a strong constitution or vigorous health; and in studies of the influence upon prognosis of a tuberculous family history nothing has been shown to indicate that it interferes with the prospect for arrestment of the disease or with recovery.

The freedom from tuberculosis of races and peoples that had as yet not been brought in contact with the disease was at one time considered an evidence of their immunity, but the error of this view has become apparent enough; and instead, it has been found that their effective exposure is followed by infection with almost mathematical certainty, and when this occurs through contact with tuberculous individuals whose disease follows an essentially chronic or favorable course, they, themselves, develop a most virulent and fatal type, showing that the virulence is conditioned by the new soil and not by its variation in the bacillus. Maffuei¹⁰ has been able to demonstrate the difference experimentally in chicks. When they had a tuberculous parentage, their infection was followed by a chronic form of tuberculosis with a tendency to recovery, whereas in those of healthy parentage, the course of the infection was acute and rapidly fatal.

The comparatively lower mortality from tuberculosis in peoples who have long battled with the disease was evident long before the introduction of modern methods of public and private hygiene. In the British Isles, for instance, a gradual reduction is shown as far back as we have reliable statistics. Similar observations have been made in other European countries, and they indicate the operation of the law of adaptation by which individuals and races increase their resistance to agencies which act destructively and threaten their

⁶ Trans. Nat. Tub. Assoc., 1907, 191.

⁷ Wien. klin. Woch., 1904, xvii, 129.

⁸ Brit. Jour. Tub., 1908, ii, 20.

⁹ Ibid., p. 35.

¹⁰ Rend. R. Accad. dei Lincei, Roma., 1903, xii, p. 421; Zentralbl. f. Bakt., 1904, xxxiv, 708.

extinction, and transmit it to their posterity. Among their posterity there must necessarily occur differences and oscillations, and in unions in which one member possesses a less degree or none at all, the offspring's resistance represents but the average. In the negro race in the United States, which has suffered severely from tuberculosis during the last fifty years, the course has become less severe, and the chronic type is now observed much more frequently than twenty or twenty-five years ago. In more recent years I have observed latent forms more often than formerly, and recoveries are no longer such rare exceptions as they were at that time.

The special resistance which has thus been transmitted may gradually disappear in subsequent generations, when the defensive functions have not been exercised, or when they have become impaired by an unhygienic mode of life, or actual disease. We see this illustrated in families in which the disease skips one or more generations, only to appear again in the next.

Higher degrees of specific resistance to tuberculosis in man must be accepted in instances of latent infections and in those in which the disease appears to have been promptly arrested in its early incipency. Such latent infections have been discovered by Loomis,¹¹ Pizzini,¹² Kaelble,¹³ Harhitz,¹⁴ Weichselbaum and Bartel,¹⁵ Spengler,¹⁶ and others, and the tubercle bacilli, though apparently without power of pathogenic action in the individuals in whom they were found, were nevertheless shown to possess it, in the animal experiment. The frequency with which these authors found such latent infections at autopsies in which no evidence of tuberculosis could be shown, and the studies of Perez¹⁷ and of Manfredi and Frisco¹⁸ preclude the assumption that the bacilli had been deposited so recently that they had as yet not time to produce their characteristic tissue alterations.

The assumption of a specific resistance is justifiable and more rational for the interpretation of some of the minute non-progressive or obsolete and healed tuberculous lesions, which are so frequently found accidentally at autopsies and so often described in literature, that I need not cite particular statistics. In many such cases the nature of the lesion was confirmed by animal inoculation, showing, as in the instances of latent infection, that the bacilli had retained their virulence. More remarkable still are examples of extensive eruptions of tubercle, even of generalization in important organs, that have followed an apparently latent course. I refer more particularly to cases of generalized milary tuberculosis in which no symptoms were produced until shortly before death, or in which a generalized affection was found accidentally at autopsy. Such

¹¹ Med. Record, 1890, xxxviii, 689.

¹² Münch. med. Woch., 1899, xxxvi, 622.

¹³ Wien. klin. Woch., 1905, xviii, 241.

¹⁴ Ztschr. f. Hyg. und Infektskr., 1903, xliii, 347.

¹⁵ Zentralbl. f. Bakt., 1898, xxiii, 404.

¹⁶ Ztschr. f. klin. Med., 1892, xxi, 329.

¹⁷ Jour. Infect. Dis., 1905, ii, 143.

¹⁸ Ibid., 1902, xxxii, 295.

cases were, for instance, reported by Hager¹⁹ and by Kollick.²⁰ In the cases of Wunderlich,²¹ or of Demme²² the entire course of the generalized disease had been symptomless, until the mechanical, irritative, and pressure effects from the coexisting meningeal tuberculosis caused death in a few hours. A mild and entirely afebrile course of miliary generalization, in which the number of tubercles or the number of organs involved offered no adequate explanation, is likewise suggestive of a specific antagonism to the bacillary toxins. If we add to such unusual observations the frequently observed healed lesions mentioned before and the spontaneous recoveries from more advanced stages of local tuberculosis, often under adverse conditions, we have better reason to consider them as evidences of a high degree of specific resistance than to ascribe them to accidents, or to freaks of Nature in which her best students know that she does not indulge.

Much more circumstantial evidence might be added to strengthen this side of the argument, but the facts stated may suffice for the consideration of the theory that man, although protected in various ways against the access of tubercle bacilli to his tissues, is primarily not resistant to their pathogenic action after an entrance has once been effected, even though his tissues be normal. The theory denies that tuberculous ancestors transmit to their descendants a specific predisposition of their tissues, by which the development of tuberculosis is favored; on the contrary, it affirms that under the law of adaptation there has been evolved a protective mechanism on the part of the tissue cells. This protective mechanism and its function differ in degree of development, and, therefore, in efficiency, according as they have been exercised more or less frequently and constantly in preceding generations and have been preserved by a normal hygienic mode of life. In instances in which the antagonism of this function is insufficient to prevent the primary localization and pathogenic action of the tubercle bacillus entirely, it may still retard its growth and modify favorably the course of the disease, thereby permitting a further increase through the specific stimulation by the bacillary products, the same as we observe it in other infectious diseases.

Without such a defensive mechanism, infections could but progress, and eventually destroy the organism. When we find this otherwise, and improvement and recovery occur, we are constrained to ascribe the contrary course to the intervention of a newly developed or increased power of defense which is also shown by the formation of specific antibodies in the blood serum. The amount and rapidity of their production varies with the infected organism itself, and with

¹⁹ Deut. med. Woch., 1881, viii, 557.

²⁰ Prag. med. Woch., 1901, xxvi; Contribl. f. inn. Med., 1901, xxii, 606.

²¹ Arch. f. phys. Heilk., 1859, iii, 283.

²² Cited by Cornet, Nothnagel's Spec. Path. and Ther., Wien, 1901, Th. 2, Abth. II, p. 41.

the biological characteristics of the related bacteria, and upon this variability depends, at least in part, the course of the disease.

When the required mechanism is present and its function is easily excited, when the amount of specific stimulation for this purpose is adequate but not excessive, then the organism protects itself promptly and efficiently; but when these conditions are not at all, or only partially fulfilled, the result varies accordingly. The mechanism and its functions are liable to be less perfected and less effective in localized infections like tuberculosis, in which the stimulus is inadequate because of the limited production and slow absorption of specific toxins from primarily small non-vascular foci; and, further, because the tubercle bacillus is but a slow grower, and is itself extremely resistant to disintegration. Under such conditions the resistance develops but slowly, and never attains as high a degree as it does in general infections. The influence upon the course of the disease is more frequently only that of a check clinically manifest by an intermission which lasts until a reduction occurs naturally in the course of time, or until adverse influences of a general nature and especially in nutrition have a like effect. Accessions and remissions follow thus, as we are accustomed to see them in the clinical course of phthisis, the former leading to further local impairment by advance of the disease.

The evolution of this function for the species as a whole must of necessity be slow, and even the attainment of a degree capable of modifying greatly the severity of the disease process, to say nothing of protecting against the infection entirely, may require centuries. Whether or not such an influence is now apparent in most of the infections with which the human race has battled in the past, as some students believe, we need not here decide, but the claim of competent observers, that infectious diseases previously unknown among a primitive race are unusually severe in their course, is suggestive.

In tuberculosis of the negro race I am inclined to the belief that the amelioration in severity in the course of the disease heretofore referred to may be considered as an evidence that a specific resistance begins to manifest itself, and if we are justified to look upon specific agglutinins for tubercle bacilli as an evidence of it, my own observations of their occurrence in apparently healthy full-blooded blacks, as well as in mulattoes, would give support to this view. Landis,²³ in a recent publication, has shown that the increase of agglutinins in chronic phthisis of negroes corresponds to that of white people, and he likewise found them present in such, who were in apparently vigorous health. Studies of immunity in tuberculosis are of more recent date and not enough comparative observations between so-called predisposed and not predisposed subjects have

²³ Jour. Med. Research, 1908, xiii, 19.

been made to corroborate fully the views here expressed. The occurrence, however, of specific agglutinins for tubercle bacilli in the blood serum of not a few persons who are apparently in good health, and with more or less frequency in newborn infants of mothers who have no demonstrable tuberculosis, would suggest a transmission of immune substances, while their almost uniform presence in tuberculous subjects shows their formation under the specific stimulus of the disease.

In the regular examinations of our patients in the Winyah Sanitarium we have practically never failed to demonstrate agglutinins excepting in cases in the cachectic stage of phthisis, although like others we have never observed a high degree of agglutinating power to develop in patients who have not been subjected to specific treatment. In cases in which the reaction occurs in apparent health in older children and in adults, it is of course possible that it stands in relation to a latent or healed tuberculous lesion not demonstrable clinically; but this could hardly be the explanation in the case of newborn infants whose mothers have no evidence of this disease. Examinations for other immune bodies in such cases will undoubtedly bring additional light as to their transmission. Being present in but small amounts in tuberculous subjects, and, as a rule, in still smaller amounts in those who are in apparent health, we would naturally expect that when transmitted the amount must be still less, and perhaps so small that they would not be demonstrable by the method usually employed.

In newborn infants Rosenberger²⁴ never found complete agglutination in dilutions higher than 1 to 1, or 1 to 3. Of the 27 infants which he tested, 15 gave no reaction at all. With a different culture of tubercle bacilli the results in another series of 39 newborn infants were positive in a still smaller number, and the almost entirely negative results of Salge²⁵ and the negative results of Descos²⁶ and of Cavazza,²⁷ and the few positive results observed by Anderodias²⁸ may, in part, have been due to unsuitable cultures.

In 8 of Salge's nurslings who were under one year of age and in whom there was a suspicion of tuberculosis, the reaction was positive. So far as concerns newborn infants the accumulated observations show that in a minority of cases agglutinins in amounts sufficient for demonstration may be transmitted by the mother, even if she be clinically free from tuberculosis.

In infants borne by tuberculous mothers the reaction is present more often, but the opportunity for making such tests is not frequently afforded to those who are most interested. (Hirigoyen²⁹

²⁴ *Centribl. f. inn. Med.*, 1904, xxvi, 665.

²⁵ *Jahrb. f. Kinderhik.*, 1906, xliii; *Schmidt's Jahrb.*, 1907, cxcv, 75.

²⁶ *Jour. d. phys. et de pathol. gén.* 1903, v, 127; *Baumgarten's Jahresber.*, 1904, xx, 571.

²⁷ *Poliein. sex. prat.* anno 11, fasc. 10; *Baumgarten's Jahresber.*, 1904, 514.

²⁸ *Soc. obstétr.* Paris, 1903, Juin 20; *Arch. gén. d. méd.*, 1903, ii, 1791.

²⁹ *Gaz. hebdom. d. méd. et de chir.*, 1901, vi, 703.

tested one case and obtained a positive result.) In the two examinations made in my laboratory the mothers had been treated specifically to within several months of confinement, and their sera had at that time attained a complete agglutinating power in dilutions of 1 to 250 and 1 to 175 respectively. The serum of their babies' blood taken from the umbilical vein showed an agglutinating power in dilutions of 1 to 100 in the first, and of 1 to 80 in the second case. In the former the serum was likewise tested for specific amoceptor by Bordet and Gengou's³⁰ method and its presence was still shown in a dilution of one part of serum in 500, this having been the greatest dilution which was prepared. Thus it would seem that the degree of specific resistance as represented by the agglutinating power of the serum at birth bears a proportionate relation to that possessed by the mother during her pregnancy.

There is, however, reason to believe that transmitted immunity becomes diminished with increasing age; for this speaks for instance the communication of Bentzen³¹ who found that of 26 nurslings not over four months of age, all of whom were exposed to measles, only 4 contracted the disease, while of 47 others exposed between the ages of five and eleven months 35 acquired the infection. Other observations upon the frequency of acute infectious diseases in nurslings have been similar. Mossé and Daunic,³² Widal and Sicard,³³ Schumacher,³⁴ Hicks and French,³⁵ Staubl³⁶ and many others have shown the presence of specific agglutinins in the blood of infants born by mothers who during their pregnancy had suffered from typhoid fever; but most of the authors also found that they soon disappeared. Anderson,³⁷ and also Polano³⁸ have shown a similar relation experimentally in diphtheria; Figari³⁹ found immune bodies in the serum of the young of immunized goats, and these were further increased by suckling.

While agglutinins belong to the specific immune bodies, the one which is of greater importance for the demonstration of a true immunity is the so-called "amoceptor" which enables the germicidal part of the blood to act upon the foreign cells or bacteria, and although both are as a rule present in immune sera, the agglutinins may disappear, while the amoceptor function remains. Neither is there a necessary quantitative relation between the two, although both usually increase under active methods of immunization.

Until more recently my own studies were limited to specific agglutinins, the method for their demonstration being less complex, less difficult, and more rapid. My records of several thousand

³⁰ Ann. de l'Inst. Pasteur, 1901, xv, 289; Berl. klin. Woch., 1906, xxxiii, 1531.

³¹ Norsk. Mag. f. Laegevid., 1905, No. 7; Ctrbl. f. inn. Med., 1906, xxvii, 17.

³² Comp.-rend. Soc. d. biol., 1897, xlix, 238.

³³ Ibid., p. 804.

³⁴ Ztschr. f. Hyg. and Infektkr., 1901, xxxvii, 323.

³⁵ Lancet, 1905, i, 1491.

³⁶ Ctrbl. f. inn. Med., 1905, xxvi, 404.

³⁷ Jour. Med. Research, 1906, x, 241.

³⁸ Ctrbl. f. inn. Med., 1905, xxvi, 714.

³⁹ Riforma med., 1905, xxi; Schmidt's Jahrb., 1906, cxcxi, 63.

tests in approximately 500 patients examined show unmistakably that a high agglutinating power corresponds with a favorable course of tuberculosis. In more recent examinations for demonstrating the specific amoceptor, I have been able to show its presence in healthy persons with and without coexisting agglutinins, and have found that the amount may be large in tuberculous patients when the agglutinins are proportionally low in amount, and that like the agglutinins the amoceptor function can be increased under the administration of specific products of the tubercle bacillus.

I must now recur to the question of general resistance and consider its importance, which I may appear to have neglected. I have, however, indicated that the formation of immune substances is a cell function, and as this depends again upon normal cell nutrition it is apparent that the general health of the individual is not a negligible factor either in prophylactic hygiene or in the treatment of the actual disease. The integrity of the natural external protective agencies by which access of the tubercle bacillus to the tissues is hindered or prevented, likewise depends upon it. Disturbances of nutrition may, therefore, suspend or lower the specific resistance, and when continued, may cause its complete loss. Such observations have been made in experimental infections, when by starving, exposure to cold, poisoning, etc., animals naturally immune to a given infection have been made to succumb to it.

Normal nutritive processes have an opposite effect in favoring the elaboration of protective substances or preventing their loss, which is especially observable in chronic infections, both by experiment and clinically, and our system of general dietetic and hygienic treatment of tuberculosis rests upon these principles. Von Hanse-⁴⁰mann has shown that they apply to plant life as well, by observing the difference between a poor unsuitable soil and a good one upon parasitic infection, the parasites disappearing spontaneously when the nutrition of the plants was improved.

Thus in the individual case in which the organism resists the infection or the progress of the disease, the lowering of the nutritive function may, and frequently does, disturb the balance in its favor, while an added improvement or the recovery of the lost balance acts in the opposite way.

The theory of specific resistance, as a substitute for a specific predisposition, tends to show that under the law of adaptation and the survival of the fittest, tuberculosis has in the course of time been changed from a rapidly progressive and usually fatal, to a chronic and more often self-limited disease, and that this is chiefly due to the development of a specific defensive apparatus against the tubercle bacillus and its toxins.

Inasmuch, however, as the efficiency of this apparatus is modified

⁴⁰ Die Deutsche Klinik, 1903, i, 665.

by its use or disuse and by the general nutritive integrity of the organism, it follows that there is little if any prospect that the disease will naturally disappear even in remote periods of the future, the less so, as, by reason of its local character, a high degree of immunity is never likely to be attained, because when effective enough to protect fully against infection in one generation, it will fail, by disuse and by unhygienic modes of life which lower it, to do this in succeeding generations. The disease must, therefore, fluctuate in frequency and severity, with perhaps a tendency on the whole to a more benign course. Reibmayr believes that upon these principles and with the aid of a better hygienic mode of life the human race must eventually work out its own salvation.

Studies in immunity since he wrote his treatise entitle us to hope that this may be anticipated by protective vaccination against tuberculosis, through which the attained resistance of the individual may be maintained and further increased. That in the manifest disease the therapeutic application of the same principle will greatly aid in securing actual and lasting recoveries, I believe to have amply demonstrated with others in the past seventeen years, since Professor Koch introduced his first crude tuberculin for this purpose. The value of this aid, although disputed and discredited by many observers, I learned to recognize in the first years of my work, and upon purely clinical observations the conviction was forced upon me then, that the action of tuberculin when properly applied was one of active immunization, limited in efficiency chiefly by the crudeness of the remedy and by the advance of the disease and coexisting complications.

Since then better preparations have become available and methods have been discovered by which their immunizing action can be shown in blood studies, which enable the observer to witness the development of immune substances and their increase to a degree which, in well-selected cases, soon exceeds manyfold that which has been shown to occur spontaneously under the much slower, and, as a rule, inadequate self-immunization through the same product derived from the bacillus and absorbed from the diseased tissues. Such studies and the permanency of clinical results have overcome the distrust in the method and have converted opponents into active supporters, and they have given a new impulse to specific treatment to a degree that I fear will once more lead to unjustifiable expectations.

Very little has as yet been attempted in the prophylactic use of specific products from which I am convinced their greatest benefit will eventually accrue, especially when we can find a still more effective vaccine and on that account also a quicker method. It is, however, quite possible that in subjects not as yet tuberculous, the present comparatively slow method can be greatly shortened, and experience must show to what degree prophylactic immunization

must be carried to assure protection against ordinary modes of infection. In the meanwhile the early glandular tuberculoses of young children, and the prophylactic application of the present method in those known to have been exposed, offer an attractive field, and in such and similar cases I have in the past seen most favorable changes in the general health and improvement in retarded physical development under specific treatment.

**A CLINICAL STUDY OF THE EFFECT OF TUBERCULIN
TREATMENT ON THE SERUM AGGLUTINATION
OF TUBERCLE BACILLI.**

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For several years the agglutination of tubercle bacilli by human blood serum has been investigated in the Saranac Laboratory, not only to see if the agglutination test is of value in the diagnosis of tuberculosis, but also to determine if the test can be used as a control during the course of tuberculin treatment. In a previous communication¹ we have reviewed the whole subject of the serum diagnosis of tuberculosis as employed by Arloing and Courmont. Our tests were made absolutely according to the directions given us by Dr. Paul Courmont in person. We found that the serum of healthy individuals agglutinated tubercle bacilli almost as frequently as did the serum of patients suffering from pulmonary tuberculosis (84.28 per cent. for healthy, and 87.09 per cent. for tuberculous persons), and that the agglutinating value in these healthy and tuberculous subjects was practically the same (13.67 for healthy, and 14.82 for tuberculous). We, therefore, agreed with Koch, Beck and Rahinowitsch, C. Fränkel, Romberg, and others, that the serum diagnosis of tuberculosis is of no value in the diagnosis of pulmonary tuberculosis. We next turned our attention to the effect of tuberculin treatment on the serum agglutination.

During his investigations into the relation of cattle to human tuberculosis, Koch felt compelled to apply the agglutination test as a means of differentiating the two bacteria, and first attempted to follow the method of Arloing and Courmont. He found, however, that their method was too complicated for practical use, and

¹ *AMER. JOURN. MED. SCI.*, October, 1906.

that it did not give uniform and reliable results. He therefore prepared an emulsion of pulverized tubercle bacilli.² When a test is made with Koch's test mixture, diluted to 1 to 10,000, it is found that the greater part of the reaction has occurred at the end of fifteen to twenty hours. In our tests we gave a limit of twenty-four hours. The length of time of the reaction, the temperature at which the tests are made, and the amount of mixture must always be exactly the same.

With this emulsion tests may be made either in the morning or afternoon. They are placed in the incubator at 37° C. over night, and then examined the following day. Serums should be used clear, and should be as fresh as possible. In all our tests serums from fifteen to twenty-four hours old were used. It is necessary that an absolutely certain macroscopic appearance be accepted as the limit of agglutination, if one desires to obtain comparable data. At the limit of agglutination there should still be present macroscopically a loose, clearly distinguishable, and evenly distributed precipitate.

In his experiments on animals, Koch found that in order to give rise to the agglutinating power, and when it is already present, to increase it, it was necessary to have marked, and if possible, strong reactions from tuberculin. Agglutination usually first shows itself several days after the injection. It reaches the highest grade in from seven to ten days and then slowly sinks. It is, therefore, necessary to make the agglutination tests in from seven to ten days after the injections, in order to obtain the highest degree.

When animals are treated with cultures of bacteria with a view to immunization, there regularly appear in their blood in addition to the agglutinating, also immunizing properties, presumably of bactericidal nature. Koch, therefore, took it for granted that in his animals, if they were brought artificially to a more or less high agglutinating power, there was produced a certain degree of immunity. He leans to the view that the agglutinating power is to be classed with the immunizing properties, and considers that the degree of agglutinating power and the immunity stand to one another in a certain relation, at least at the beginning of the immunizing process, and that the agglutinating power is a standard for the grade of immunity produced.

There is produced from tuberculosis under natural conditions no, or very little, resisting substance in order to permit it to come to cure and resulting immunity. The question forced itself upon Koch, namely, after it is possible, with comparative ease, to raise in animals the agglutination and amount of resisting substances so extraordinarily, whether it is not possible, by means of artificial production of resisting substances, to assist the human organism in

² Deut. med. Woch., 1902, Nr. 88.