ology, course, and prophylaxis of "tropical diseases." Each advance indicates more clearly that the greater number of these diseases are infectious and consequently may be prevented, and that each step in preventive medicine renders the tropics more habitable for races accustomed to temperate climates. Our increased knowledge of tropical diseases enables us to identify, in temperate climates, diseases—such as ankylostomiasis, filariasis, etc.—which, without the knowledge so acquired, would escape recognition. Thus at home, in a temperate climate, we are exposed to many so-called "tropical diseases."

As a result of modern interest in the tropics, of modern research in regard to the dissemination and prophylaxis of "tropical diseases," the monumental work of the late Major Walter Reed, United States Army, must be cited.

Lastly, as our knowledge of "tropical diseases" increases, the importance of their geographical and meteorological relations diminishes, and the conclusion is reached that they are equally as important to the medical men of temperate climates as to those of the tropics.

W. J. Calvert.

TRYPSIN. See *Pancreas.*

TRYPTOPHAN (PROTEINOCHROMOGEN).—In their classic work on "Die Verdauung nach Versuchen" (1831) Tiedemann and Gmelin noted the peculiar red coloration which pancreatic juice and the intestinal contents of animals gave with chlorine water. Claude Bernard failed to observe the reaction with *fresh* pancreatic juice. The researches of Kühne and his followers have indicated that the color reaction is due to a product of the cleavage of proteids, especially through the agency of pancreatic digestion. Kühne found that the characteristic reaction could be obtained equally well with bromine water, which is now more generally used in testing for the substance. If a mixture containing the rose-colored product of the reaction be shaken with amyl alcohol the colored product is taken up by the latter solvent and shows in this a characteristic spectroscopic absorption near the D line. The name *tryptophan* (from θρύπτομαι and φαίνω) was introduced by Neumeister as indicating the origin of the body in the decomposition of proteids. Stadelmann applied the less familiar term *proteinochromogen*, reserving the word *proteinochrome* for the colored compound of which the halogen (Br) forms a part. Trytophan is now known as a typical and constant product of the tryptic digestion of proteids. It may also arise when the albuminous substances are split up by baryta water, dilute acids, or the action of bacteria. When proteids are digested with purified pepsin or papain (?) it is not obtained. Glaessner has shown, however, that it is formed by the enzyme pseudopepsin, which is associated with true pepsin in the gastric membrane. Tryptophan may arise in the autolysis (self-digestion) of tissues, even in the absence of bacteria. The vegetable enzymes bromelin (from the pineapple) and nepenthin (from Nepenthes), as well as those from many other plants, also form products which are said to give the violet color with chlorine or bromine water.

In the earlier attempts to isolate and identify tryptophan, the chromogen was precipitated from its solutions in the form of the halogen compounds which are obtained with bromine or chlorine. The results were not constant, and the products of different investigators varied in their composition, owing to the difficulty of separating them completely from other decomposition products of the proteids, such as peptones. Accordingly various analyses have been reported which showed the compound to contain carbon, hydrogen, nitrogen, and bromine (or chlorine). Pyrrol and indol derivatives were obtained as decomposition products. Nencki regarded tryptophan as the mother substance of some of the pigments (melanins, etc.) which have their origin in the animal body. The latter yield similar products of cleavage.

Tryptophan was first isolated as such by Hopkins and Cole. In composition it corresponds with the formula $C_{11}H_{12}N_2O_2$; and it has been identified as skatol-amido-acetic acid, which Nencki believed would be found as the precursor of those indol derivatives that arise during the putrefaction of proteids. The pure, colorless crystals show great proneness to undergo brown pigmentation on heating with acids, or even with water alone. Tryptophan thus isolated gives the well-known Adamkiewicz proteid reaction (with glacial acetic acid and concentrated sulphuric acid), which has been shown to depend upon the presence of glyoxylic acid in the acetic acid used. Solutions of the isolated tryptophan also give the "pine-slip" reaction direct, offering strong evidence of the presence of the pyrrol ring (or the indol nucleus). The investigations of Ellinger have made it probable that tryptophan is a precursor of indol in the putrefaction of proteids, and that it thus bears a direct relation to the indican of the urine.

For the methods of isolating tryptophan, the reader is referred to the papers of Hopkins and Cole. To test for tryptophan in solutions containing products of proteid decomposition, the following method is usually employed: The solution is acidified with acetic acid, and gradually treated with two or three volumes of saturated bromine water until a reddish-violet precipitate is formed. Large amounts of proteid may first be separated by precipitation with alcohol. The tryptophan is then searched for among the alcohol-soluble products, after removal of the alcohol by evaporation. *Lafayette B. Mendel.*

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TUBERCULIN. See *Tuberculosis.*

TUBERCULOSIS.—An infectious disease caused by the bacillus tuberculosis.

HISTORICAL.—It is possible to divide the literature of tuberculosis into six periods. 1st. The description of the tubercle as a specific structure. 2d. The early clinical and anatomical study of phthisis and other lesions of the disease. 3d. The discovery of the infectiousness of the disease and the proof by this of the etiological unity of the lesions. 4th. The discovery of the bacillus and the proof that it was the cause of the disease. 5th. The discovery of tuberculin. 6th. The study of modes of infection and the part played by animals in the extension of infection.

1st. Although the word tubercle had long been used to designate a small nodule, it was not until 1793 that it was described by Bailey as a specific structure. He described under this name a special formation which he found in the lungs in cases of phthisis. The tubercles are small round bodies, never exceeding the head of a pin in size, and which are formed in the cellular tissue of the lung. Large tubercles can be formed by the union of small. The centres of the large tubercles are converted into pus, and this transformation of tubercles into abscesses is the cause of phthisis.

2d. Bayle in 1811 made an anatomical study of phthisis based on one hundred and nine autopsies. He defines as phthisis all lesions of the lungs which produce disorganization and destruction of the lung tissue. He characterizes phthisis clinically as an *ensemble* of symptoms consisting in cough, dyspnœa, marasmus, hectic fever, and sometimes purulent expectoration. Anatomically he distinguishes six varieties of phthisis, but gives special importance to the first two, tuberculous phthisis and granular phthisis.

In tuberculous phthisis the lung contains tubercles formed of an opaque homogeneous substance having a whitish-yellow or grayish color. These tubercles are at first firm, but they afterward soften in their centre, and are finally destroyed by suppuration. The tuberculous affection is a chronic disease of a special character, but probably of a scrofulous nature, and should not be regarded as the result of inflammation. The second variety, granular phthisis, often accompanies the first. In this the lungs are filled with miliary transparent granules of cartilaginous hardness, from the size of a millet seed up to that of a grain of wheat. These granules are not exclusively localized in the lung, but may be met with in the peritoneum, intestine, and heart. This is the first description of miliary tuberculosis.

In 1826 Laënnec proclaimed from his study of pathological anatomy the unity of the different forms of phthisis, and he found the characteristics of the disease in the evolution of the tubercle. "The progress of pathological anatomy has demonstrated that pulmonary phthisis is due to the development in the lungs of a peculiar formation which has received the name of tubercle. The tuberculous material develops in the lungs and in other organs in two principal forms, as isolated bodies and as infiltrations. Each of these forms presents a number of varieties due chiefly to their different degrees of development. The isolated tubercles present four varieties which may be distinguished as miliary tubercles, crude tubercles, granulations, and encysted tubercles. The tuberculous infiltration presents three varieties which can be designated as crude tuberculous infiltration, gray tuberculous infiltration, and yellow tuberculous infiltration. Whatever may be the form into which the tuberculous material finally develops, it presents in its origin the appearance of a gray or semitranslucent mass which gradually becomes yellow, opaque, and very dense. It finally softens, becomes almost as fluid as pus, and is expelled by the bronchi, leaving in its place cavities commonly known as ulcers of the lung, and which we designate as tuberculous excavations." Laënnec also recognized the specific character of these lesions. "One cannot regard the tubercles as the result of inflammation of some one of the constituents of the lung without destroying the results of observation and making a strange abuse of reasoning. If inflammation has any influence on the appearance or the development of the tubercles, it is only to prepare the soil and make it favorable to their growth; in the same way as the soil when cultivated after a long repose will germinate a multitude of seeds which have lain in it for a number of years."

The views of Laënnec prevailed generally until the more careful anatomical investigations of Virchow. In his work on the lymph glands Virchow says: "More careful observation shows that the scrofulous affections of the lymph glands are secondary, and not due to any preceding blood crasis or any general change in the character of the blood, but secondary in relation to the local changes of those parts from which the glands obtain their lymph. The gland swelling is due to certain substances produced in consequence of pathological processes, which are carried over in the lymph to the next lymph nodes and produce in them similar irritation. This can take an inflammatory character or a progressive development without evidences of inflammation. The condition is called scrofula when slight irritation produces extensive glandular swellings. In certain individuals the swelling continues, and this is the reason why it appeals to some as an independent process. The condition is connected with a weakness of the individual or of certain parts of the body. This constitution can be acquired, as is shown by the frequency of such conditions in prisons, where the nutrition of the inmates is not sufficient. The signs of this weakness are a diminished capacity of resistance of the tissue toward disturbances and slighter powers of recuperation." After describing the caseation of the products of inflammation in the lymph glands he says: "A similar condition can take place in the inflammatory products of a mucous membrane when these remain for a considerable time at the place of their formation. They also become thickened and caseous. This takes place in no other part so often as in the lung, where the alveoli and small bronchi become filled with such caseous masses, and that condition arises which, since Laënnec, has been given the name of tuberculous infiltration, and which I consider as caseous infiltration or caseous hepatization. This may involve entire lobes of the lung, or it may be limited to single sections of the lung and then corresponds to what is ordinarily described as crude tubercle. Sometimes it is limited to small groups of lung alveoli; then it is miliary caseous hepatization. There is nothing that justifies us in considering these masses as tubercles. Along with this, tuberculosis can take place, but the tubercles are seated in the walls and not in the lumen of the air passages."

Virchow described the tubercle on the other hand as an organized structure, a neoplasm. It has a cellular structure, but is not vascular. It arises from the proliferation of pre-existing structures and is never an exudation. The larger tubercles are formed from the union of a number of small tubercles. These sharp, precise views of Virchow represent a great advance.

They were purely anatomical, and based on his studies of the histogenesis of pathological processes. His knowledge of microscopic structures enabled him to separate a new formation of tissue from an exudation. It was perfectly logical from such a study to make the distinctions which Virchow made. Laënnec's idea of the unity of the process was based on similarity of the gross appearances, and he was probably also influenced by his clinical knowledge of the disease, finding the same general clinical course in the various types of the lesions. There is no histogenetic unity of the tuberculous lesions, the only unity is the etiological one which was given by the work of Villemin and Koch.

3d. The infectiousness of the disease. Koch in his work on tuberculosis gives Klencke (1843) the credit for the discovery of its experimental transmission, but says he did not continue his experiments, and they were forgotten. Klencke's experiments on tuberculosis were undertaken in accordance with his idea that contagion was carried by pathological cells which have the power of generalizing an affection. He says he has been able to transmit cancer and melanosis, by intravenous injection of the cells, from man to the dog and cat. The tuberculous cells are capable of being transplanted in the same way. Tuberculous cells prepared by one of his assistants were introduced into the jugular vein of a rabbit, which when killed six weeks afterward showed extensive tuberculosis of the liver and of the lungs. The rabbit served to inoculate a crow, but without result. Although there is no doubt that Klencke did succeed in transmitting the disease, it in no way detracts from the credit of Villemin. Villemin (1865) showed that rabbits inoculated subcutaneously with tuberculous material from a man, from a cow, and from a rabbit became tuberculous. At the end of twenty to thirty days the animals began to emaciate and finally died in a state of extreme cachexia. The autopsies showed tuberculosis of the lymphatic ganglia and a formation of tubercles in the viscera and on the serous membranes. Cohnheim, in his celebrated address on tuberculosis, gives Villemin the credit of the discovery. He says: "At this time a discovery was made in France which not only marks an incomparable advance in the history of tuberculosis, but from which must date a complete change in the general conception of the process. There have been few discoveries which have so influenced medical thought as Villemin's proof of the transmission of tuberculosis. Wherever scientific work was carried on, head and hand were set in motion to repeat Villemin's experiments and to prove his views."

In 1868 Chaveaux produced tuberculosis in three heifers by giving them, by the alimentary canal, tuberculous material from a cow. He confirmed the work of Villemin and concluded that the alimentary canal constituted in cattle as in man an important channel of infection, and one more common than the air passages.

4th. The first publication of Koch in which he described the tubercle bacillus, its mode of culture and relation to the lesions of the disease was made in 1882, and was followed by a further paper in 1884. This is the most important contribution to our knowledge of the disease, and ranks among the most important contributions to medical knowledge. It marks the beginning of an enormous increase in the literature of tuberculosis, and did more than any other publication to stimulate research in infectious diseases. The structure and the histogenesis of the tubercle were studied by animal experimentation. The presence of the bacillus and the capacity of producing the disease experimentally were shown to be the criterion of what was tuberculosis. Every doubt as to the unity of all processes in which the bacillus was found, however varying their anatomical characteristics might be, was removed. The term scrofula disappeared from medical nomenclature.

5th. No less stimulating was Koch's discovery of tuberculin in 1890. He considered this the active chemical substance which was produced by the bacilli, to which important symptoms and lesions were due. The high hopes which he had of tuberculin in the therapy of the disease have not been entirely realized, but, from the work which the discovery of tuberculin stimulated, our knowledge of the disease has been greatly increased. More attention was directed to the study of the bacillus and its varieties.

6th. In the last period of the literature, which is not marked by any special publication and may be said to begin about 1898, attention has chiefly been directed to the study of the comparative pathology of the disease, modes of infection, and immunity. Methods of diagnosis have been made more accurate, the importance of early diagnosis has become more appreciated, and rational systems of prevention and treatment have been inaugurated.

The Bacillus.—The bacillus tuberculosis is a small, non-refractive, rod-shaped organism, generally from 2 to 2.5 μ in length, or from one-quarter to one-third the diameter of a red blood corpuscle. It is not motile, is usually slightly curved, and both in the lesions and in sputum is more often found in small groups than singly, the small groups of two or three bacilli representing those which were contained in a single cell. There is considerable variation in the morphology. Organisms are found which are much longer or shorter than the ordinary forms, and in recent years a number of observers have described, both in sputum and in old cultures, long, branched, and club-shaped forms similar to the branched forms of the diphtheria bacilli. In many cases the bacilli do not stain homogeneously, but represent a striking alternation of unstained and brightly stained points, resembling a short chain of streptococci. Such forms are frequently found in the sputum, and the unstained points have been considered to be spores, but there is nothing in the life history of the organism to justify us in the belief that spores are produced, nor do the unstained areas have the refraction so characteristic of spores. This irregular staining is best shown by staining the bacilli intensely with fuchsin and decolorizing with sulphide of soda. The bacilli stain with difficulty. Staining reagents seem to penetrate with difficulty, but when stained they retain their color under conditions in which other bacteria are decolorized. It is this property which enables their detection and differentiation from other organisms. The best method for their detection in fluids is staining with carbol fuchsin with following decolorization in Gabbet's stain (two-per-cent. alcoholic solution of methylene blue in twenty-five-per-cent. sulphuric acid). In tissues they are best stained by the method of Kühne, which consists of staining in warm carbol fuchsin, using hæmatoxylin as a counter stain and decolorizing in Orth's discharging fluid.

Their detection in sputum is a matter of great practical importance, for it is on this that the diagnosis of lung tuberculosis is principally based. The morning sputum coughed up by the patient should be examined. This should be spread out on a dark plate and the more opaque consistent particles picked out and spread on a cover slip in a thin layer. The cover slip is then dried and heated over a flame to render the albumen insoluble. Several drops of carbol fuchsin are placed on the dried surface, the cover slip is then boiled over the flame and placed in Gabbet's fluid for one to two minutes for decolorization and counter stain. The bacilli are usually fairly abundant in the sputum of cases of lung tuberculosis, and there is no difficulty in their detection. Occasionally small, hard masses may be found in the sputum, especially in cases of advanced tuberculosis with cavity formation, which are entirely composed of tubercle bacilli, and which represent pure cultures of the bacilli growing on the walls of the cavities. I have several times seen such masses in the sputum after the use of tuberculin. The positive diagnosis of the absence of bacilli can be made only after repeated examination of carefully selected portions of sputum, or by boiling the sputum in two-per-cent. caustic potash and examining the sediment. The sputum may also be digested in pancreatin and the sediment examined. In the lesions in the tissues the bacilli occur in extremely variable numbers, and the examination of numbers of sections may be necessary to detect them.

There are few bacilli with which they may be confounded. They closely resemble the leprosy bacilli, but it can rarely happen that the question of differential diagnosis from these can come up. The leprosy bacilli stain with carbol fuchsin in the same way, but they also stain with the ordinary bacterial stains. There is much more danger in confounding them with other bacteria of the acid-resisting group, such as the smegma bacilli and a bacillus frequently found in hay and in dairy products. There can be little doubt that these bacilli have been frequently confounded with the tubercle bacillus, the former in the examination of urine, and the latter in the examination of dairy products. The tubercle bacilli can be distinguished from these by the fact that they retain their color in alcohol after they have been differentiated, while the smegma and the hay bacilli are decolorized. There may even be difficulties in the inoculation test, for the hay and butter bacilli produce in rabbits and guinea-pigs nodules which closely resemble tubercles, though they lack the characteristic caseation.

The tubercle bacillus was first grown in pure culture by Koch on solidified blood serum. But little can be added to his description of the growth. In from ten to fifteen days the first sign of growth appears as dull white points or specks on the surface. These cling lightly to the surface and appear as dry scales. According to the amount of material used for inoculating the surface, the abundance of bacilli contained in it, and their distribution on the surface, there is a greater or less extent of surface covered by the scales. At first the single scales are separate, but finally they become joined and form a thin grayish-white coating over the surface. On transplanting to fresh tubes more bacilli are carried over, they are more homogeneously distributed, and the growth forms a connected membrane. The extension over the surface is not caused by the wandering of the bacilli, nor by the bacilli piling over the edge, but by the membrane being shoved over the surface by the continual growth. The bacilli never liquefy the serum, nor do they grow into it, but always remain on the surface. At the edge of the growth the small masses of bacilli have peculiar forms when examined under the low power. They grow in fine, bent, or curved lines, often having the shape of the letter **S**. The ends of the masses are pointed and the middle is swollen, giving them a spindle shape. When the bacilli are very numerous in the tissues they may appear in masses having this form. Such masses may be seen in the walls of tuberculous cavities of the lungs and in the tubules of the kidneys. (Plate LVI.)

EXPLANATION OF
PLATE LVI.

EXPLANATION OF PLATE LVI.

FIG. 1.—Section from the Lung in a Case of Miliary Tuberculosis. *a*, Tubercle containing numerous bacilli; *b*, tubercle with fewer bacilli; *c* and *d*, tubercles with cheesy centre and containing no nuclei; *e*, cross-section of a blood-vessel surrounded by a deposit of pigment. Magnified 50 diameters.

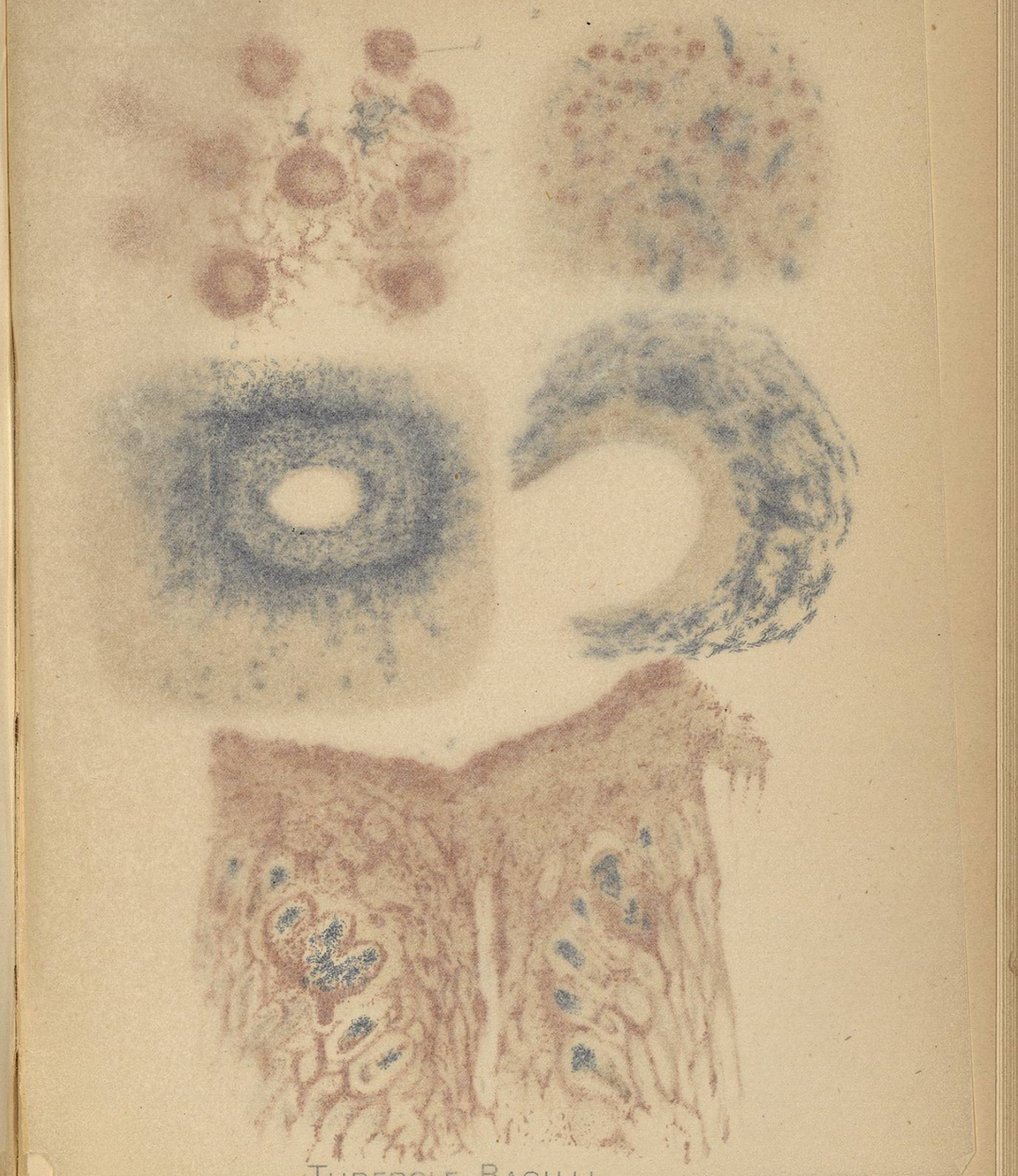
FIG. 2.—The Blue-colored Portion of the Tubercle *a* in Fig. 1. The tubercle bacilli are stained blue, the nuclei of the cells brown. Magnified 700 diameters.

FIG. 3.—A Small Artery surrounded by a Mass of Tubercle Bacilli. From a bronchial gland in a case of miliary tuberculosis. Magnified 100 diameters.

FIG. 4.—A Portion of the Wall of the Artery shown in Fig. 3. Magnified 500 diameters.

FIG. 5.—Section from a Phthisical Lung, showing the Crowding of the Tubercle Bacilli into the Alveoli. Magnified 100 diameters.

Plate LVI.



TUBERCLE BACILLI.

FROM R. KOCH'S "DIE AETIOLOGIE DER TUBERCULOSE"
Mittheilungen aus dem Kaiserlichen Gesundheitsamte. Berlin, 1884.

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