shall have to be content with the demonstration that the symptomatology bears the character of a parasitic infectious disease.

As it is not possible to discuss all the questions belonging here in connection for all diseases, I have brought them together in each affection under the head of "General Pathology."

The second part of our task will consist in tracing the connection of the local new-formation with the pathogenetic parasite. This requisite, I believe, it will be possible to fulfil exactly as regards the leprous disease. In general, the following axioms may be maintained: The local effects caused by the immigrated bacteria may be traced back to two factors, which indeed are very changeable in their importance for the pathological process in the several affections; now one, now the other preponderating, perhaps also one not becoming obvious at all. *But in every case the final product, the effect, for every species of bacteria is a specific one; the pathological processes in themselves have absolutely no specific character.*

1. One of the above-mentioned factors is an alteration of the vessel walls of the blood and lymph channels, especially the lymph sheaths inclosing the large vessels, leading to inflammation. Lymph-cells, white blood-corpuscles accumulate in the tissue, to serve, in their further stages of development, in the building up of the tumor. The process of cell production in itself, therefore, is not specific, and hence we cannot speak of a "specific inflammation." *But the future destination of the cells furnished by the vessels, which serve as the raw material, is specific for every form of disease and directly dependent upon the specific qualities of the respective virus.* There comes in question here, first, the acuteness of the inflammatory cell production and its relation to the vascular development which may proceed in more or less adequate proportion; second, especially the direct, immediate influence on the several cells exerted by the immigrated bacteria. These modify the normal course of the inflammatory connective-tissue development in a specific manner, so that either an intermediate stage of the progressive cell development is maintained for a very long time, or specific degenerative processes run their course in the cells.

2. The virus acts not only on the vessel walls, inciting inflammation, but the tissue itself is implicated. Our knowledge of these "tissue processes" is still very slight, and relates in but a few points to the vascular connective tissue. Of the nerves, muscles, and glands we know only that they have perished in certain stages. Only in a single case (formation of the primary induration in syphilis) we shall have to speak of *productive* implication of the fixed connective-tissue cells. (The "granulation cells" we trace back, as above stated, to inflammatory lymphoid cells.) Otherwise we have to deal only with *necrobiotic* processes which are excited by the virus at an earlier or later period, in the connective tissue and its vessels.

There is no "specific" implication of the epithelium. Although the latter is frequently—especially in the initial stages—found very largely increased, it furnishes no characteristic signs of the respective granulation-cell tumor.

Thus we have to deal essentially with an inflammatory process in the connective tissue. The course of this inflammatory process, however, is an abnormal one by the influence of these very parasitical formations. It does not lead to new formation of connective tissue—but, whether by an alteration suffered at any time by the cell material itself or by the vascular development requisite for the nutrition of the cellular neoplasm, sooner or later the "tumor" perishes by the same organisms which have caused it.

The acuteness and the malignancy of this process depend directly upon the qualities of the instigators of the infection.

According to the infectious materials, we distinguish the following groups.

1. Tuberculosis.
2. Leprosy.
3. Syphilis.
4. Frambœsia tropica.
5. Glanders.
6. Actinomycosis.

As regards mycosis fungoides, we lack as yet every landmark on which to base the assumption of an infectious disease; according to its structure and its clinical course, it decidedly belongs to our class.

On the other hand, I certainly hold that lupus erythematosus does not belong to this group. The inflammatory cellular infiltrations occurring in it are inconstant, and at any rate do not form the essential feature of the pathological process; perhaps lupus erythematosus, like psoriasis, belongs to the epithelial affections.

I. TUBERCULOSIS, SCROFULOSIS, LUPUS.

General Pathology.—At the present time, tuberculosis, and with it scrofulosis, is the best-known chronic infectious disease of man, and the only one demonstrated with certainty.

Villemin was the first to class tuberculosis as an inoculable infectious disease; but his doctrine failed to secure universal recognition. Further inoculation experiments were made by different savants in the most variable manner. The experimenters introduced the material into the animals from all possible points, so that the following result was rendered certain. If tuberculous material be transferred to an (appropriate) organism, there is developed in it, in a typical manner, a tuberculosis which sometimes remains more local, at other times spreads through the body generally. Only specific tuberculous material is capable of communicating this disease. Non-tuberculous matters, or those deprived of their infectious quality, *never* produce tuberculosis. It was shown at the same time that the "predisposition" of some classes of animals was variable as regards the receptivity for the disease.

Klebs described a form of micrococcus as peculiar to tuberculosis and cultivated it. In the same way, Schüller has reported experiments in cultivation and inoculations with its result. A landmark has been furnished also by the interesting experiments made by Deutschmann, who, by leaving at rest inoculable tuberculous pus, separated it into a light wine-yellow serum inactive in inoculation, and a thick, tenacious sediment which produced tubercle. Recently, Damsch, in Ebstein's clinic, has been able to demonstrate tuberculosis of the urinary passages in the living, by successful inoculations into the anterior chamber of the eye of rabbits. Aufrecht alone has described microscopically specific bacteria in the tissues, without having been able to gain general recognition of his results.

But the credit of having finally elucidated the nature of tuberculosis belongs to Robert Koch, who furnished the incontrovertible proof that *a specific bacillus is the cause of tuberculosis and of scrofulosis.*

The proof consisted, first, *in the demonstration of a parasitic micro-organism in tuberculous neoplasms.* For this a new staining process had to be invented which culminated chiefly in the fact that alkaline solutions were alone appropriate. The method originally devised by Koch was very soon modified by Ehrlich, who found the alkalescence-producing factor in anilin oil (or, according to Ziehl, in carbolic acid). His procedure is as follows: The sections, or else the dry preparations made on covering glass and suf-

ficiently warmed, are stained in a mixture produced by the addition of a concentrated alcoholic fuchsin or gentiana-violet solution to a watery, well-agitated and filtered aqueous solution of anilin oil (carbolic acid solution). In this the preparations are left for a *long* time, *best several hours*, or a short time in *heated* solutions, are then freed from superfluous color in alcohol or water, and are then immersed in a solution of one part of officinal sulphuric (or nitric) acid with two or three parts of distilled water. The deep blue (or red) color gives place at once to a faint yellow, the stain being bleached in all parts of the tissue. *The bacilli, however, retain the color and may now be recognized under comparatively low power* (Hartnack obj. 7). It is better to subsequently stain the background with anilin brown or methylene blue, because then the blue or red bacilli can be more easily distinguished. The preparations, after having been dehydrated in alcohol, are rendered transparent in oil of cloves and preserved in Canada balsam. The preparations are not always permanent, the color of the bacilli gradually fading, probably because the acid is not thoroughly washed out. The gentian preparations are certainly more constant in their color than the fuchsin preparations. The color keeps best when the specimens (dry preparations) are not at all inclosed in Canada balsam, but are directly examined in oil of cedar (with homogeneous immersion).

The bacteria rendered visible by this method have a rod shape, hence are bacilli. Their length corresponds about to one-fourth to one-half the diameter of a red blood-corpuscle. Their breadth differs according to the method employed; Koch's original methylene blue renders apparent only the exceedingly slender bacilli, while Ehrlich's and Baumgarten's staining processes color also the sheath inclosing the bacillus. Characteristic of the tubercle bacilli, in Koch's older method, is their rejection of the anilin brown staining after they have already taken the methylene blue. In Ehrlich's method, the tubercle bacilli retain the tint present in the anilin oil and are not decolored by acid or subsequent methylene blue staining.

The bacilli are found in great numbers *wherever the tuberculous process is of recent inception and in rapid progress;* then they usually form closely packed small groups often arranged in bundles which lie largely *within* the cells. Besides, there are also numerous free bacilli; especially at the border of large cheesy patches they are present in large free swarms. After the acme of the tubercular eruption has been passed, the bacilli become sparser and can be seen only isolated, often as faintly colored, probably dying or dead formations. If giant-cells are present, the bacilii are found most numerously within them. Here, too, those with bacilli are the more recent, those without them the older cells in which the bacilli originally present have died or have passed into a subsequent dormant state. Besides the ordinary bacillus forms, we find others with two to four oval spores which are placed at regular intervals along the bacillus.

Subsequent examinations, wherever made, confirmed the correctness of Koch's statement as to the constant presence and the diagnostic value of these bacilli in tuberculous affections.

But even this did not satisfy Koch himself. He said: "It does not follow, however, from this coincidence of tuberculous affection with bacilli that both phenomena stand in causal relation to each other, though no slight degree of probability for this assumption is furnished by the fact that the bacilli are found chiefly wherever the tuberculous process is in its inception or progress, disappearing where the disease comes to a standstill." "*In order to prove that tuberculosis is a parasitic disease caused by the immigration of the bacilli and is originally due to their growth and increase, the bacilli must be isolated from the body and cultivated in pure fluids until they are freed from any possibly still adhering morbid product derived from the animal organism, and finally, by the introduction of the isolated bacilli into animals, the same morbid picture of tuberculosis must be produced which experience has shown us to result from inoculation with tuberculous matters of natural origin.*"

This task Koch has performed in a brilliant and absolutely unobjectionable manner (despite Spina's demurrer).

The cultivations were made in sterilized, coagulated blood serum. They were distinguished by an exceedingly slow growth which proceeds only at a temperature of 37–38° C.; they form minute compact scales which can be easily detached in toto and by appropriate examination are shown to consist only of the well-known, extremely delicate bacilli. The cultivations yielded corresponding results, whether the matter was derived from animal or human tuberculosis; they were continued for months outside of the animal body, by successive transference from serum to serum.

But in every case inoculations of healthy animals with the cultivations yielded a positive and constantly uniform result—a typical inoculation tuberculosis of the animal.

In guinea-pigs the inguinal glands swelled after two weeks, the points of inoculation on the abdomen changed into an ulcer, and the animals emaciated. After from thirty-two to thirty-five days the animals were killed. They all exhibited intense tuberculosis of the spleen, liver and lungs; the inguinal glands were greatly swollen and cheesy, the bronchial glands were only slightly swollen.

In the same way rabbits, rats, cats, dogs, etc., were successfully inoculated. The experiments with rats and dogs are especially interesting because these animals have otherwise shown themselves uncommonly resistant toward inoculations of tuberculosis.

The result of the experiments is independent of the point of inoculation: subcutaneous connective tissue, anterior chamber of the eye, abdominal cavity, direct introduction into the blood current, etc. Only it is necessary, owing to their exceedingly slow growth, that the infectious matters be brought to a spot where, protected from external injury, the bacilli have the opportunity to increase and penetrate into the tissues, otherwise the bacilli are again eliminated before they secure a habitat. "Small shallow cutaneous incisions are no wounds appropriate to the invasion of bacteria. Similar conditions will be requisite to insure the adherence of the bacilli which have reached the lungs. Probably, factors favorable to the retention of the bacilli, such as stagnating secretions, denudation of the mucosa of its protective epithelium, etc., will be of assistance in effecting the infection."

It appeared, furthermore, that the rapidity of the course of inoculated tuberculosis, as well as its extent and spread over the several organs, is dependent upon the larger or smaller quantity of infectious matter introduced. The picture of acute miliary tuberculosis occurred only when the body was at once overwhelmed, as it were, by a large quantity of infectious germs. Otherwise, when but few bacilli are inoculated, the processes are of slow development or circumscribed locally (nodules on the iris, opacity of the cornea, affections of the lymphatic glands), which are very much later succeeded by general inflection, unless the disease terminates altogether with the local processes.

There remains to us the task of maintaining for our limited field the principal points, as well as isolated experiences to be utilized by their analogy with lepra, syphilis, etc. They are:

1. Tuberculosis—*i. e.*, that disease of sometimes acute, sometimes chronic course, attended with the formation of small granulomata—arises from the infection with a specific kind of bacteria, the above-described bacilli.

2. The parasites transmitting the infection are always derived from an animal organism, and are transferred more or less directly from one organism to another. Outside of the animal body, the bacilli or their spores may retain their infectious character for a time; but they cannot multiply outside the animal body (except under conditions for special culture), like the bacillus anthracis.

3. For infection, the bacillus requires undisturbed development at a protected place. On the skin and the mucous membranes, a lesion of the protective epithelial covering is an indispensable prerequisite. The delicate endothelial covering of the pulmonary alveoli, with the larger openings of the lymph-channels between the cells, and also the surface of the iris, seem to permit entry of the bacilli into the plasmatic channels without mechanical lesions. The local process at the point of infection ("primary effect"), according to observations hitherto made, is the following:

After an incubation of from eight to fourteen days, a nodule forms at the point of inoculation, which either increases without rupturing or, generally, changes into a shallow dry ulcer. Very soon (often simultaneously, it appears) the neighboring lymphatic glands swell, and then already, as a sign of the constitutional affection, appears the great emaciation leading in two more weeks to rapid death.

No certain deductions can unfortunately be drawn at present as to the relation of the local infection to the general disease, especially as to the precise time when the latter commences, and whether the latter depends upon a local tuberculosis at the point of inoculation. Noteworthy is the almost synchronous affection at the point of inoculation and that of the neighboring lymph-glands, which is succeeded by the general eruption in the other organs; here again there is a regular anatomical connection between the last-attacked organs and the formerly affected lymphatic glands.

4. The acuteness of the development and the course of tuberculosis are dependent mainly upon the quantity of the infectious material introduced each time. A greater resistance peculiar to some classes of animals (rats, dogs) is second in importance, but is not absolute, and is overcome by inoculations with cultivated bacilli, that is, large quantities of them.

5. The question whether tuberculosis continues to spread by heredity is still *sub judice*. Theoretically, the possibility that the bacilli migrate from the maternal into the fœtal organism, or that a direct bacterial infection of the ovule or the semen occurs, must at once be admitted in analogy with other infectious diseases (syphilis, relapsing fever, the corpuscular disease of silk-worms); nor is this heredity very rare, if we follow Baumgarten, the most recent author on this question. He pointed out that processes now recognized as tuberculous were not formerly acknowledged as such. Besides, there is the large number of "scrofulous affections which come under observation in the first months of life on the post-mortem table and in the living, and which render their fœtal origin very probable."

In our opinion, this intra-uterine origin does not form the rule. On the contrary, in the great majority of the cases we have to deal with an extra-uterine affection occurring after birth.

This variation, this irregularity in the hereditary transmission, though we cannot understand it at present, finds its analogy in syphilis; also in variola, vaccinia, etc., in which the hereditary infection likewise occurs at times and at others does not.

But how can we explain those frequent observations of tuberculous affections of hereditarily "tainted" persons.

Two modes of explanation are possible: either tuberculosis itself, or a predisposition

to it is transmitted. According to the former view, the phthisical habit would be actual tuberculosis; whether subsequently an active disease develops is said to depend upon external influences which sometimes favor, sometimes prevent the increase and spread of the bacilli. The other party admits the physical habit to be the consequence of tuberculous disease of the parents, a developmental anomaly resulting from it, but not latent, undeveloped tuberculosis. (For instance, this bodily conformation may be transmitted to later generations, but without any tuberculosis.) In order that genuine tuberculosis should develop, a later affection with bacilli must indubitably be superadded.

An individual so constituted is sickly, less resistant to noxious influences, but not tuberculous until infected with tubercle. Only this danger of infection with the bacilli is greater with such "habit" than in healthy persons (as a rabbit is more prone to it than a dog); and a further factor is superadded in that such people of "phthisical habit," *i. e.*, inherited inability of resistance, are usually precisely in the environment which especially increases the possibility of infection—surrounded by tuberculous parents and relatives, that is, centres of infection. Hence it will have to be carefully weighed whether the bulk of the affections hitherto ascribed to heredity should not more correctly be traced to infections within the family.

Baumgarten, however, firmly adheres to the doctrine of heredity. In the first place, he correctly points out that tuberculosis is not only a disease of early and middle age, but also of infancy. "On the contrary, scrofulosis, which must be looked upon as one of the manifestations of tuberculosis, is an almost exclusive privilege of childhood." That from such foci, which remain harmlessly in the body for years, a more acute form of tuberculosis may subsequently result has indeed nothing remarkable in it, to our thinking. But where there is an absence of such symptoms peculiar to tuberculosis, which are plainly perceptible in childhood, Baumgarten will have us assume "latent" foci, an "insidious tuberculosis of hidden organs" existing from earliest infancy, which is derived in the uterus from the parents (in whom the tuberculosis may likewise be "latent"); a view which he endeavors to prove by very copious material. On the other hand, we shall have to take into consideration the fact that a large number of tuberculous affections in infants, formerly considered to be hereditary transmissions, are possibly traceable to infection with the milk of gargety, *i. e.*, tuberculous cows.

We hold, therefore, that hereditary and intra-uterine transmission of tuberculosis is possible, but that the extra-uterine infection with specific bacilli forms the rule.

Koch's investigations, furthermore, have confirmed what had been taught already by a number of previous attempts at inoculation: That a large proportion of the affections termed scrofulosis (and the pearl disease [garget]) are indeed true tuberculosis. It must be left to further investigation to sift from an etiological point of view the great number of processes which are to-day simply called scrofulosis, often not to be distinguished histologically, and to separate true tuberculous from non-tuberculous affections traceable to other noxa.

In what manner, under the influence of the bacilli, does the patho-anatomical product arise which we call tubercle?

The tuberculous process is induced by the influence of the immigrating parasites (1)

on the vessels which become inflamed by them and (2) on the tissues which suffer injury in a manner as yet unknown. A localized inflammation is developed which leads to the formation of a nodule consisting of round cells and permeated by the reticulum of the ordinary connective-tissue fibrillæ. Now, while this nodule represents nothing peculiar either in its structure and its cell-forms, or in the manner of its origin (and can be recognized as tuberculous only by the inclosed bacilli), it takes a specific course under the influence of the tuberculous noxa. In the beginning, it enlarges by successive cell accumulation at the periphery, and vessels gradually extend into the mass. But then, *i. e.*, very early, a modification commences at the point of attack of the virus, namely in the centre of each single depot. Not merely the exuding inflammatory cells, but also the tissues deteriorate there; the cellular protoplasm coagulates, the nuclei lose their capacity for staining, *i. e.*, the cells exhibit the typical picture of a necrosis of coagulation (Weigert).

The vessels and the basis substance of this central depot become likewise implicated in the necrosis, and thus is developed that specific form of tissue degeneration which is known as cheesy degeneration (in Weigert's sense) and must be distinguished from inspissated pus deficient in water. Around the cheesy centre are found, however, some progressive developmental forms of the inflammatory round cells: large, bright, epithelioid cells with large nuclei, and those known by the name of Langhans' giant-cells. (These are not situated, as Ziegler assumes, typically in the centre, but rather at the periphery of the tubercle.) Some are inclined to look upon Langhans' giant-cells as exclusively confined to tuberculous processes. Others bring them into relation with the growth of the vessels, interpret them as abortive vascular new-formations, as it were, at the border of the cheesy and still viable cells. With Ziegler, it appears to us at present most probable to look upon the development of the tubercle cells and their various stages (like their origin), not as specific processes, but as developmental forms, such as occur in all inflammatory neoplastic processes, in their further course. Thus it may be that the marginal position of the nuclei stands in a more intimate relation with the specific nature of the tuberculous virus (perhaps also with an incipient necrosis of the central protoplasm of the giant-cell).

Specific in the tubercle is the cause which furnished the cellular material by way of inflammation, and the manner of its destruction: the "caseation" beginning in the centre of each nodule and thence progressing peripherally. A patho-anatomical distinction between specific caseation and other cheesy masses is not always possible. Altough tuberculosis always leads to caseation, the latter, inversely, does not in every instance coincide with tuberculosis.

Specific, furthermore, is the subsequent spread of the tuberculous process into the neighborhood. In syphilis or leprosy, "local" recoveries by way of total absorption or inflammatory connective-tissue encapsulation are the rule; in tuberculosis they belong to the rare exceptions. For instance, the typical formation of callosities around gummata is not effected; a small-celled inflammatory zone arises around each tubercle; but the infection extending into it hinders the final, fibrous connective-tissue formation and effects the opposite, progressive caseation, that is to say, the tuberculosis migrates into the tissue. At times, of course, this destructive process is a very slow, insidious one; Baumgarten, too, justly calls attention to the fact that the local malignancy of tuberculosis is greatly overestimated, as we not rarely can demonstrate in the lungs, the lymphatic glands, etc., tuberculosis which has become "latent" at least for years.

The above delineation of the patho-anatomical process has gained some important supports in the discovery of the bacillus.

1. The bacilli are always found in greatest number at the periphery of tuberculous processes.

2. They are largely situated within the cells, especially in giant-cells. But I do not believe that, as Koch assumes, the bacilli are inclosed as foreign bodies in the giant-cells; on the contrary, I think that the immigration of the bacilli into the exudation cells excites the latter to that—atypical—morphological development which we call giant-cells.

3. The bacilli finally lead to the death of the cells, whereby they themselves perish as bacilli, but probably maintain the infectious character of the necrotic masses of tissue by means of the persistent spores.

In connection with tuberculosis (and scrofulosis) we intend to treat of lupus. It will be our aim, first, to defend the view that lupous disease is a partial manifestation of tuberculosis.

At the outset it should be explained here that I am not able as yet to furnish the exact proof of this connection, inasmuch as the bacilli of tuberculosis have not been demonstrated in lupous material. Schüller has recently published the discovery of micrococci in lupus tissue.

By anilin staining, treatment with acetic acid or potash lye, he discovered micrococci, especially in the smaller and most minute lupus nodules. Between and around the cells the micrococci lie in the form of small roundish granules, but from there penetrate as small rows into the neighboring connective tissue, never as compact masses, but rather loosely and scattered. In the larger, fully developed lupus nodules, micrococci are much more difficult of recognition, owing to the density of the cells. The more recent the lupus formation and the softer the underlying tissue, the more numerous are the cocci, especially at the wall surrounding the larger lupus nodules. To me it appears not impossible that Schüller may have mistaken the granulation of Ehrlich's "mast" cells for hives of micrococci.

However, the demonstration in the tissue of tubercle bacilli, which at best are stained with difficulty, appears to me only a question of time.

Despite careful examinations, no essential histological difference has been found between a caseating miliary tubercle and a lupus nodule. In both formations there is a patch of round cells with epithelioid and giant-cells; there are vessels in the peripheral segments of the nodules; and a central, non-vascular, coagulative-necrotic zone; both have in common the irresistible spread in the tissue and the local relapses.

The resemblance in histological structure between tuberculosis and lupus was first pointed out by Virchow (Onkol., II.), then by Auspitz. Subsequently Friedländer defined lupus directly as a local tuberculosis of the skin. Baumgarten, however, reaches the conclusion that lupus and tuberculosis should be kept apart. Although he considers both as granulation tumors in Virchow's sense, he enumerates the following essential differences:

1. Caseous necrobiosis, always present in tuberculosis, is absent in lupus.
2. The formation of epithelioid cells is less conspicuous in lupus.
3. On the other hand, giant-cells are generally present in such quantity as to form a striking contrast to the sparsity with which they are contained within true tuberculous nodules (of the conjunctiva).