

but at the same time proliferations of the interstitial connective tissue. The transverse striation becoming less distinct, and particularly more delicate, we demonstrate swelling and increase of the nuclei of the muscle corpuscles, small accumulations of from six to eight nuclei taking the place of a single one. The interstitial connective-tissue processes begin with the aggregation of cellular elements; subsequently we find only more copious wavy connective tissue between the ever sparser muscles, and finally an interstitial deposition of numerous fat-cells. According to my examinations, a fatty metamorphosis of the muscular substance *per se* does not occur.

The atrophies in question affect in the first place the muscular structure of the hypothenar, then the thenar eminence, the interossei, furthermore the deltoid and quadriceps cruris, the muscles of the calf and face. Mimetic expression disappears; the folds of the face are distorted by the contraction of isolated, non-atrophied muscular trabeculae. The eyes can no longer be closed, on the one hand on account of the pendulousness of the lower lid, on the other because of the disappearance of the muscles. The globe itself suffers under these alterations; tears flow, ulcerations of the cornea occur. The lips become flabby, the lower one drops away from the gums and allows the saliva to escape.

The hands, incapable of any activity, are clawed by the greater power of the flexors. The gait is slow, dragging; the thighs can be lifted but slightly forward; and the toes always scrape along the floor.

Finally all motion of the extremities becomes impossible, and therewith commences an exceedingly deplorable condition for the patients which is protracted for years.

Therefore, in *lepra nervorum* the essential feature is not the paralysis of motor nerve-fibres, but the atrophy of the contractile substance. Nor have we to record any disturbances of co-ordination, although the anaesthesia of the skin, going hand in hand with the motor weakness, now and then simulates morbid pictures resembling tabes. (Thus most of the patients cannot manipulate with the hand except by the aid of the sense of sight.) There is no vertigo when the eyes are closed.

C. Finally we have to treat of the complex of symptoms described as *lepra mutilans*. In later stages of the local processes, after anaesthesia, analgesia, and atrophy have been long established, there occur on the extensor surfaces of the joints shallow, slightly suppurating, indolent ulcerations. The disintegration extends into the depth, implicates the ends of the bones at the joints, and finally attacks the joint itself, and without any particular manifestations of reaction the part situated periphally from the joint—phalanges, a whole finger, even an entire hand—is cast off. Indeed, in this way are produced the most remarkable deformities, especially of the hand. Or else the ulceration establishes itself on the sole of the foot, causes extensive penetrating destruction which leads to greater or less mutilation of the foot, and now and then gives rise to serious complications by the pyæmia, erysipelas, etc., starting from it.

In conclusion I repeat that to me it appears that in the production of mutilation the complete anaesthesia has more to do than a trophoneurosis, although the latter is not to be altogether excluded.

In thus closing the description of the symptomatology, we shall again point out that there is no regular succession of the several symptoms and symptom-groups, or at most it can be fixed only within the very widest limits. At first there is a predominance of the symptoms of irritation (painfulness, hyperaesthesia, bullous eruptions, abnormal pigmentations); later they are found only isolated on formerly unaffected regions; while the zones first attacked are subjects to anaesthesia, analgesia, loss of pigment, atrophy of the sweat-glands, of the adipose tissue, of the muscles, and finally to mutilating ulcerations.

In addition to this we have the fact that the process taking place in the nerve, the chronic perineuritis, attacks the primitive bundle irregularly, "and this explains how in the same nerve region some parts are insensible, others sensible, and how of nearly adjoining muscles one atrophies and the other is preserved." (Virchow.)

With this group of phenomena may be associated other symptoms not directly connected with the leprosy. The sexual function may become impaired. The bodily temperature falls, the patients have a permanent chilly sensation. The heart's action languishes.

The course of *lepra anæsthetica* in general is slower than that of the tubercular variety, and it leads to death from exhaustion and marasmus.

The prognosis, therefore, as regards the duration of life, is somewhat better than in the tubercular form; but the fate of the patients is far more deplorable.

PATHOLOGICAL ANATOMY.—As is well known, Virchow was the first to call attention to the anatomical alterations in the nerves. We fully coincide with Virchow's view and place the primary pathological process in the peripheral and cutaneous nerves, in which a leprosy new-formation leads to compression and atrophy of the sensory and trophic fibres. The patho-anatomical demonstration of this atrophy has recently been furnished especially by Leloir, who points out the existence of a parenchymatous neuritis by the side of the interstitial neuritis, leading to total atrophy of the nerve-fibres. According to him, this degeneration of the nerve-fibres depends not always directly on the interstitial process, but may also occur primarily.

While all authors admit the existence of these peripheral processes, there is still some uncertainty whether they are to be interpreted as the primary ones, or whether there is not rather a central affection, springing from the brain and cord. In fact, there are on record by various authors some positive post-mortem demonstrations of changes in the spinal cord. Opposed to these observations are a number of purely negative examinations, so that I am more inclined, owing to the constancy of the peripheral changes and the inconstancy (and in positive cases not specifically leprosy character) of the central lesions, to regard the nervous form of leprosy as a disease of the peripheral nerves.

Most frequently affected are the ulnar, median, radial, musculo-cutaneous, intercosto-humeral, and peroneal nerves.

On the bones we find mainly necroses together with carious processes and interstitial absorption.

Between the two, the cutaneous and the nervous forms of leprosy, is a whole series of mixed forms. Indeed, it may even be asserted that there is hardly any pure case of strictly cutaneous or purely nervous leprosy, although it is possible to separate the cases clinically according to the most prominent symptoms. As "mixed" forms, then, we shall have to record the cases lying about midway between the two. Observation teaches that a case may also change its position; for instance, being tubercular in the beginning of the affection, and later becoming "mixed" by complication with nervous symptoms.

This variety is also the more frequent one; namely, the mixed forms are usually at first tubercular with subsequent disease of the nerves, more rarely the "anæsthetic" forms become "tubercular" afterwards.

Leprosy prevailed already among the Jews and the Egyptians, as appears from Exodus. Hippocrates was acquainted with the disease, but only from descriptions.

In Greece it became more frequent in the last two centuries before Christ.

In Italy, in the second century of our era.

Thenceforth the spread was rapid over the greater part of Europe.

In France, we find leper houses in the seventh, in Germany in the eighth century; as early as 757, edicts against marriage were published.

The disease reached its greatest spread at the end of the eleventh century on account of the crusades. It is said that there were 2,000 leproseries in France and 19,000 throughout Europe. Founding of the order of St. Lazarus for the care of the leprosy.

In the course of the sixteenth century, leprosy in Europe disappeared more and more, while at the same time syphilis spread epidemically.

Since then the geographical spread can be almost positively traced to the introduction of the disease from countries affected with leprosy.

GENERAL PATHOLOGY.

The new-formation characterizing leprosy is found most frequently and in its most extensive development on the external skin and the mucous membranes, in the shape of circumscribed nodes or in more diffuse infiltrations (both in the tubercular and in the macular form, which latter is considered a stage preliminary to the nodes).

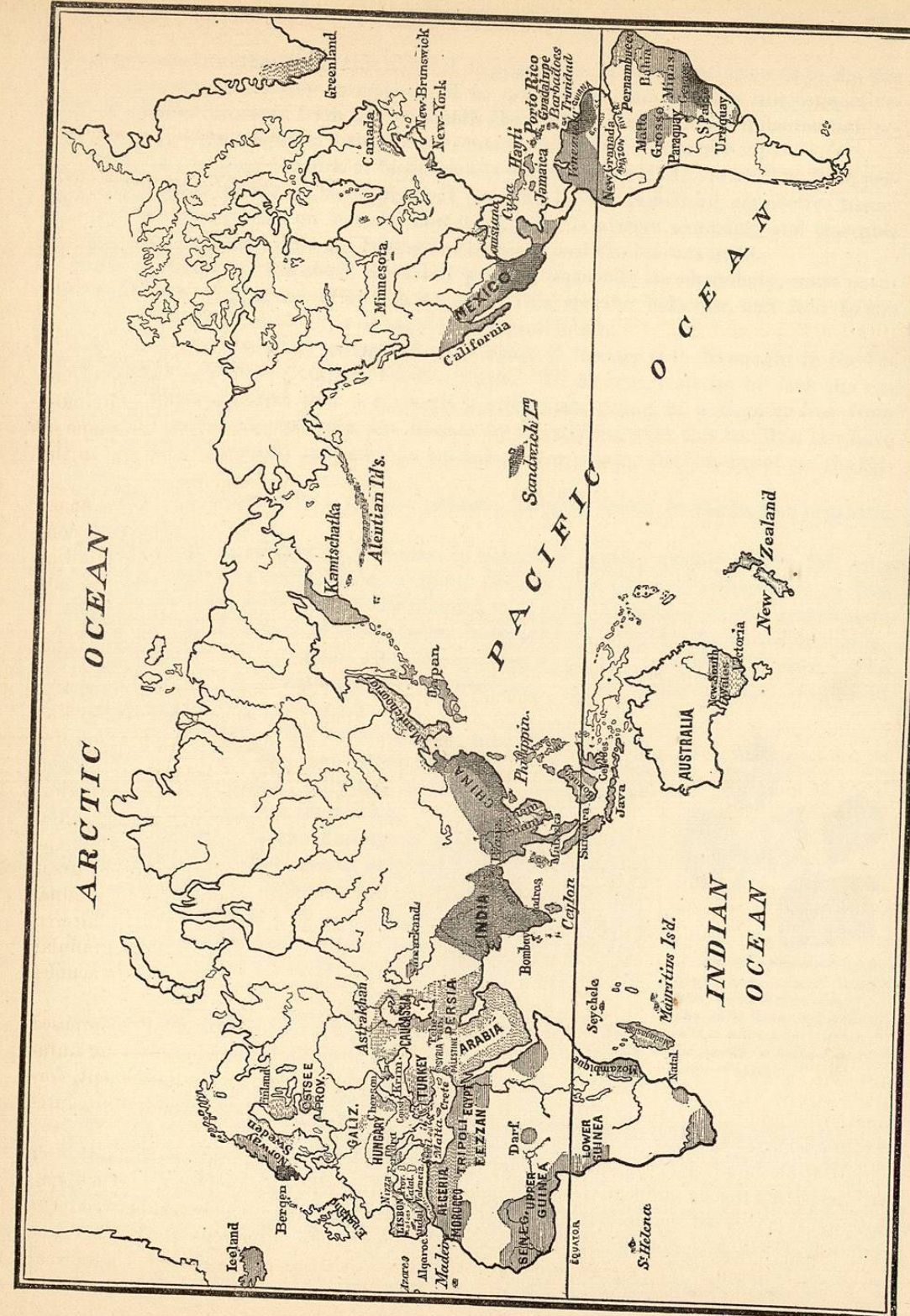
Opposed to the tubercular form stands lepra nervorum, the so-called lepra anæsthetica, in which Virchow demonstrated the proliferation in the interstitial nervous connective tissue resembling that in the external cutaneous nodes. We are also familiar with new-formations in the substance of the cornea, and with such as penetrate into cartilage and are indicated in the interstitial tissue of the spleen, liver, etc. The lymphatic glands and the testicles are likewise very intensely attacked. (But I should not refer these alterations in the last-mentioned organs to interstitial proliferating processes.)

All these neoplasms show a corresponding structure; a cell-mass separated by sparse fibrillary intermediate tissue; the cellular elements, in their recent condition exactly like lymph-corpuscles, gradually increase in size, the body of the cell reaching four or five times its original volume, the nucleus likewise undergoing material increase, and now and then several nuclei are present in a single cell. The form of the cells in the great majority of cases is round; the spindle shape of the mostly large protoplasmic bodies is found more sparsely. The neoplasm, which is traversed by abundant blood-vessels, and in the neighborhood of which the cellular accumulation is most dense, is distinguished by great persistence, may remain for years, but finally disappears almost completely by gradual absorption, leaving deep-brown, pigmented, slightly thickened, otherwise little altered skin. Before the complete degeneration, we find on the large, pale, slightly granular cells forming the neoplasm in this stage a peculiar phenomenon: "a species of vacuoles is developed," bright, spherical lacunæ in the compact cell-mass.

In these lepra nodes, therefore, we have to deal with a tumor originally composed of ordinary granulation cells—a tumor the cells of which possess a remarkably long duration of life, in a certain sense present stages of further development: enlargement, formation of giant and spindle cells; finally, after a period of vacuole formation, disintegrate and vanish.

But at the place of the former tumor, a flat thickening and elevation of the skin or of the subcutaneous connective tissue remain behind. This thickening, *i. e.*, the deposition of masses of connective tissue, is very pronounced on the nerves, between the bundles of which we find, in the later stages of the process, numerous thick trabeculæ of fibrillary tissue. The circumference of the nerves at these points exceeds the normal considerably (spindle-shaped swelling), the quantity of the nerve-fibres, however, is remark-

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ably diminished, so that from this alone it is possible to draw a conclusion as to the size of the connective-tissue new-formation. I do not believe, though, that this connective-tissue formation proceeds from the lepra cells themselves, but from the inflammation occurring around the neoplasm (which represents nothing but a foreign body).

There is a copious network of blood-vessels within the swelling; after they have perished, large concretions of blood-pigment are left in the remaining connective tissue. The ulceration occurring on nodular new-formations is always secondary and traceable to external factors, and does not belong to the history of the leprous node.

The peculiarity of the above described process, especially its chronicity, must naturally give rise to the inquiry after the cause of this specific behavior, and lead to the search for noxæ, of chronic type or capable of reproduction.

We personally decidedly assume that the cause of leprosy is to be sought in the existence of a specific bacterium, the bacillus lepræ. To be sure, thus far we lack the experimental demonstration that a formerly healthy man, living in a country free from leprosy, has become affected with the disease by inoculation with this bacillus, nor have the experiments absolutely succeeded in animals. Our reasons for this belief are the following:

I. The bacillus lepræ is a specific parasite, hitherto found in the human organism only in leprosy.

It is met with in all leprous processes, in nearly all organs, usually within the cells constituting the new-formation, more rarely free in the tissue; furthermore, in free hives in the purulent secretions of disintegrating nodes. Examined in the recent state or in unstained preparations of tissue (after hardening in alcohol), the bacilli are recognizable with difficulty; but easily after the staining of sections in any anilin color. The staining succeeds less readily with dry preparations. (The bacilli are best stained in solutions of pigment in anilin oil.)

After the staining, the covering-glass may be rinsed in acidulated water; they are then dried and mounted in Canada balsam. By this method, only the lepra bacilli remain well stained, other bacteria lose their color.

Very interesting is the finding of bacilli in dry leprous nodes of the skin and the mucous membrane merely inclosed in paper, as described by Köbner. In sections from tissue thus preserved, the bacilli are so conspicuous above the unstained fundamental substance that Köbner specially recommends this drying of the nodes as an excellent method for the study of the bacilli.

The micro-organisms thus rendered visible are exceedingly fine thin rods; now and then tapering on both ends, of one-half to three-fourths the length of a red blood-corpusele. Their breadth is one-fourth or less of their length.

Thus it will be seen the bacilli of leprosy bear a remarkable resemblance to those of tuberculosis. But they are distinguished from each other by their staining relations. The bacillus of tuberculosis can be stained only in alkaline solutions of pigment, while the bacteria of leprosy can be tinted easily also in neutral and acid solutions: gentiana, fuchsin. Only with anilin brown it has been impossible hitherto to color the bacilli of leprosy.

Instead of a slender entire bacillus, very frequently small granular particles are

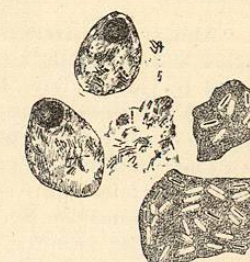


FIG. 23.—Lepra cells with bacilli and isolated bacilli with the formation of spores. The dark flakes are stained cells in which the envelope of the bacilli is visible in the shape of lacunæ.

found. These are either products of degeneration—and then the granules are irregularly scattered in the protoplasm of the cell, coarse and variable in size—or else the granulation is the sign of a progressive act, the formation of spores. The latter consists normally in the occurrence of oval, non-tingible formations, two or three in number, which break the continuity of the rod like lacunæ. (Under, as I believe, unfavorable or abnormal conditions of growth, it seems that also spherical swellings of these spores develop at the ends and in the course of the bacilli.) Characteristic, moreover, is the presence of a comparatively broad mucous envelope, easily rendered visible in dry preparations stained with watery anilin solution (fuchsin, gentiana violet, etc.). (Comp. *Virchow's Arch.*, p. 526, 527.)

Another mode of growth, which I have observed both in cultures (on blood-serum gelatin) and with lepra nodes introduced into the abdominal cavity, is the lengthening of the bacilli into threads, which are about four times the size of an ordinary rod. The formation of spores in these threads did not differ from that in the short rods. Cornil claims to have observed such threads also in organs, the anatomical structure of which, showing cavities and fissures, permitted this growth. (Cornil's results should not be interpreted as threads, but merely as closely aggregated single bacilli.)

II. The bacillus is constantly present in all forms and varieties of leprosy in all countries.

Apart from the investigations of Armauer Hansen, the real discoverer of a micro-organism in lepra, there are on record descriptions of the bacillus lepræ by myself (material from Norway, Spain, Brazil, Roumania, Palestine, Hindostan, Dutch Guyana, Batavia); A. Hansen (Norway), Cornil (Spain), Hillairet, John Hillis (British Guyana), B. Hernando (Spain), Köbner (Brazil), Atkinson (North America), Majocchi and Pellizari.

Hansen examined the juice from freshly-excised cutaneous nodes. He found:

"Almost exclusively round cells, a few with fat-granules, many finely granular (called by him 'yellow and yellowish-brown elements'). Others contain small rod-shaped bodies which are partly limited by parallel lines, but in part taper at both ends, in which latter case their thickness in the middle is about twice that of the other bodies. Similar corpuscles are also found free where the pressure of the covering glass has formed small lakes, surrounded by dense accumulations of cells; in this lake of serum the corpuscles move in the manner of bacteria. Other preparations are produced in the following way: A drop of distilled water is placed on the slide and examined with a Hartnack's immersion No. 9 to see that it contains no formed elements, then the cut surface of the nodes is scraped with the knife as before, and the scrapings spread in the drop. In such preparations a much larger number of the small corpuscles appear, which here move also far more rapidly. The greater part of the cells swells considerably in the water, and in these swollen cells the rod-shaped bodies are far more easily observed; some appear as if garnished with them, at first sight it looks as if the cells were filled with coarse granules, but on accurate focussing it is seen that these apparent granules are small oblong rod-shaped particles."

The accuracy of these observations we shall acknowledge to-day without reserve. But the proof which was still lacking was furnished by me in September, 1879.

III. In every single case of leprosy, the bacillus is found in all more recent new-formations of the skin, the mucous membranes, the cornea, in the cartilage, in the interstitial nervous connective tissue; also in the connective tissue of the spleen and liver; finally, in the lymphatic glands, the testicles, and epididymis.

In these organs they are found in quantities corresponding to the degree of the affection.

With the onset of symptoms of absorption of the neoplasm, the bacilli also exhibit

corresponding signs of degeneration; disintegration into irregular granules; finally, total disappearance, when the new-formation has vanished.

A. The bacilli of the skin are present both in the nodules and in the more diffuse infiltrations.

The bacilli lie almost exclusively within the large round lepra cells described by Virchow, which, separated only by a fine connective-tissue framework, are closely packed. These cells, often exceeding the volume of a pus-corpuscle five times, contain one or several (three to twelve) large bright nuclei, greatly resembling those of the epithelial cells, and very frequently appear crowded unsymmetrically toward one wall of the cells.

The bacilli and their descendants either fill the entire protoplasm of the cells diffusely or, more frequently, there are several small circumscribed accumulations of from two to seven longitudinally apposed rods. Now and then two or three lie lengthwise one after another, presenting the appearance of a long, though not straight filament. Or else, the bacilli pushing in all directions over each other, form such a compact pile that its composition of foreign organisms can be recognized only on close inspection. Especially in those cells we encounter, beside the slender smooth bacilli, numerous shorter rods and finely granular particles.

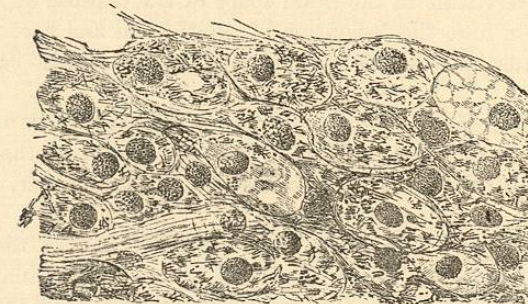


FIG. 24.—Section from a lepra node. Power=Zeiss' oil immersion 1/12, with eye-piece No. 4.

The deepest cellular layer, *i. e.*, that in the subcutaneous connective and adipose tissues, contains, together with many unchanged lymph-cells, the most recent and smallest tumor cells with relatively few bacilli in the protoplasm. Gradually ascending, the cells enlarge.

The oldest layers touch a stratum of subepidermal connective tissue which separates from the infiltration of the corium, the epithelial layer running in a straight line and deprived of its descending rete cones, but otherwise normal and merely strongly pigmented.

Most numerous in this uppermost layer are peculiar large, round, sharply-limited accumulations which untinted present a strong waxy lustre, but in anilin colors take an almost homogeneous deep stain. The anilin preparations teach that these globi represent merely cells very densely infiltrated with bacilli (and their products), and caused to degenerate. These globi correspond to the "yellow flakes" described, many years ago, by Hansen in older leprosy nodes of the skin, the spleen, and the testicles.

Besides the large lepra-cells, we see traversing the infiltration in longitudinal streaks small connective-tissue cells which here and there are infiltrated with bacilli and then form rather larger spindles than usual, and small cells differing in nothing from migratory cells; the latter free from bacilli. The presence of free bacilli between the cells in the connective-tissue trabeculæ is very limited.

However, I could never demonstrate bacilli with certainty in the blood-vessels. But the entire arrangement of the infiltration is governed by the framework of the ascending blood and lymph vessels. This connection of the vessels and the cell mass inclosing them cylindrically is especially clearly displayed by transverse oblique sections, while the smaller vessels, extending in the centre of the infiltration, remain without any special influence on the distribution. In the subcutaneous adipose tissue, the lobular arrangement prevails.

B. These descriptions referring to the skin so completely cover the conditions in the mucous affections of the mouth, palate, and larynx that their delineation would be nothing but a repetition.

C. Examination of the mucosa of the larynx also taught that both the epiglottideal and the thyroid cartilage had suffered an invasion of bacteria. Starting from the perichondrial connective tissue, the slightly-enlarged, spindle-shaped cells of which contained numerous bacilli, chains of round cells always infiltrated with bacilli could be followed in the reticular cartilage between the cartilage-cells. Free rods were also seen in the tissue of the reticular cartilage. At the thyroid cartilage, the perichondrium of which likewise contained bacilli, only free bacilli immigrated into the substance of the cartilage and finally were visible in the inner space of the capsule of the cartilage by the side of the nuclei. Even here the formation of small globi had been effected. In these preparations the intermuscular connective tissue of the larynx also contained bacilli and globi.

D. The appearances in the cartilage most closely resemble those of the cornea "which was made opaque by an immigration of lymph cells directed from the margin toward the centre. All these cells contained minute rods which were, however, also found isolated, penetrating between the lamellæ of the cornea."

E. The presence of bacilli in very large numbers in the testicle I was able to demonstrate in five subjects. I found the fungi within the canaliculi of the testicle and in the intertubular tissue. Once they were also in the epididymis. While in the cells of the canaliculi the several bacilli were still clearly visible, the lumina of the canals of the testicle were filled with a compact mass. In unstained sections they had a beautiful yellow, glossy, flaky appearance, as if composed of single amber beads; stained in anilin colors they took a uniform tint and it could be recognized that these flakes were nothing but dense accumulations of bacilli and their products of degeneration.

F. Cells containing bacilli were likewise found in the interacinous connective tissue of the liver in recent interstitial hepatitis. Cornil describes them also within the liver cells proper.

G. I have examined two specimens of the spleen and found isolated foci of bacilli in the shape of small heaps situated near the follicles, joined to large cells.

Of the kidney I have examined but a single specimen. It showed intense amyloid degeneration with interstitial nephritis. No bacilli or specific alterations could be detected. Köbner likewise could demonstrate no bacilli in the urine.

H. All the lymphatic glands examined showed very extensive infiltrations of bacilli in the peripheral zones, in which blood pigment, even macroscopically visible, was accumulated in quantities. The interfollicular tracts especially contained large multinuclear, polygonal cells with bacilli.

I. In a small portion of lung were found cheesy necrotic patches without the fine bacilli; but many long chains of bacteria immigrated, I believe, post mortem.

K. Of special importance, however, is the finding of bacilli in the peripheral nerves;

for thereby we trace with certainty to a single pathogenetic noxa the former clinical duality of the tubercular and anæsthetic symptoms. In most of the nerves formerly examined by me my endeavors to fill this gap were futile, because I always had under observation old terminal forms of disease. And that the bacilli finally perish we need not emphasize specially, after the experience gained on the skin. Just as, in my first communication, I had interpreted the "yellow masses" which I had seen in Christiania with Prof. H. Heiberg, as agglomerations of bacilli, so I was now in the fortunate position, by the death of a leprosy patient from an intercurrent acute disease, to demonstrate on recently affected nerves the identity of the interstitial process of the peripheral nerves with the leprosy new-formation in the skin, and show the presence of bacilli in the large cells between the nerve fibres and bundles. (Hansen raises the objection that these results would be valid only for the nerve alterations in the tubercular form. But it rests with him to prove the difference he supposes to exist.)

In the same way I hold that the theory advanced by Leloir and Hoggan, that lepra nervorum is a primary disease of the nerve-fibres and not an interstitial inflammation with subsequent secondary pressure atrophy of the nerves, lacks adequate support because those authors examined only nerves which had been long diseased. The fact which contradicts my view, that accumulations of bacilli are stated to be absent in such nerves, is devoid of force, because these conditions can be studied only on recently affected nerves.

L. The bacilli are absent, however, as far as investigations to date teach, in the spinal cord, in the muscles, and take no part in the production of the bullous (pemphigus) eruptions and in the affections of the bones and joints. Nor do we hold these processes to be primary, direct leprosy affections, but derive them from the primary nerve lesion as secondary symptoms.

The bacilli are absent, besides, in all epithelial tissues of the skin (rete Malpighii, hairs, glands). Loss of hair and glandular atrophy are brought about in a purely mechanical way by the compression exercised by the leprosy neoplasm. But even the covering layer of the rete Malpighii never contains bacilli; between the new-formation developing in the corium and in the connective tissue of the papillary body on the one hand, and the epidermal investiture on the other, there always remains the free sub-epidermal zone; and as the epithelial covering is inaccessible from within to any invasion of the bacilli, so it is from without.

IV. It is possible to demonstrate microscopically as well as experimentally that with the presence of the bacillus lepræ the typical course of development of a migratory cell into a connective-tissue cell suffers that alteration the result of which we briefly term "lepra cell" since the time of Virchow.

Strictly, this point is divisible into two subquestions: 1. Whence do the cells originate? Virchow had considered the fixed connective-tissue cells as the mother cells of the subsequent granulation tumor. As opposed to this view which can neither be proved nor disproved with certainty, we maintain that the granulation cells are emigrated white blood and lymph corpuscles.

2. How does a white blood-corpuscle develop into a lepra cell?

In reply to this question, I recapitulate the results of my investigations from my treatise above mentioned (*Virchow's Archiv*, Bd. 84, pp. 534 and 535) as follows:

A. Examination of the wound granulations springing up on the loss of substance caused by the excision of a broad cutaneous tubercle.

In a vertical section the lower layer appears very rich in cells in comparison with the upper. The latter is also free from blood-vessels, while they are quite numerous at the base and of great