

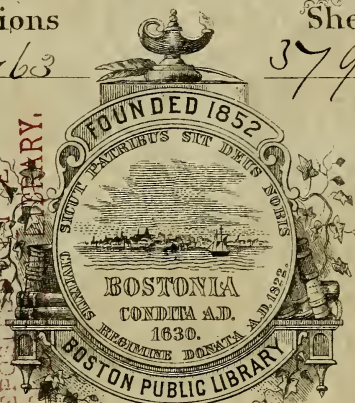
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HISTORY

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OF

TUBERCULOSIS

From the Time of Sylvius to the Present Day

BEING IN PART

A TRANSLATION, WITH NOTES AND ADDITIONS, FROM THE GERMAN OF

DR. ARNOLD SPINA

CONTAINING ALSO AN ACCOUNT OF THE RESEARCHES AND DISCOVERIES OF DR. ROBERT KOCH AND OTHER RECENT INVESTIGATORS

BY ERIC E. SATTLER, M. D

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No other event in the history of the investigation of disease has at once attracted such universal attention and interest as did the announcement by Dr. Robert Koch, in 1882, of the discovery of the *bacillus tuberculosis*. The alarming prevalence, the obscure origin, and the almost invariably fatal termination of tuberculosis, render a better knowledge of it most highly desirable.

It is the aim of this volume to supply a history of the study of tuberculosis from the earliest times to the present day. The records of the investigations relating to this subject are scattered every-where throughout medical literature, especially in the periodical journals. To discover and compile all these fugitive data was no easy task.

The first five chapters of this work are a free translation, with a few notes and additions, of the first part of the very valuable work of Dr. Arnold Spina, titled "Studien über Tuberculose," which has just appeared in Germany. Dr. Spina is the first assistant in the laboratory of Prof. Stricker at Vienna, and is a most formidable critic and opponent of the theories of Koch.

The sixth and seventh chapters are new. Spina brought his history down only to the time just preceding Koch's experiments. These two chapters contain an account of the investigations of Koch and of the various subsequent experiments of other investigators, and their attempts to verify or to overthrow his conclusions. They include a full description of the latest experiments of Dr. Spina, in which he claims to have disproved Koch's theories. A sketch of Koch's reply to Spina is given also.

The last two chapters supplement the work of Spina, and render this volume a complete history of the study of this disease up to date.

This is the first attempt to give to English-speaking readers a work of this character. The book lays no claim to the title of a compendium, aiming only to furnish a condensed, but at the same time an exhaustive, review of the most important literature relating to this subject.

It is hoped that the volume will be found valuable to the busy practitioner, who has little time to ransack numerous journals and volumes for information, and also to the student just beginning the subject. To him who is inclined to go into a special study of tuberculosis, the copious references to original sources of information will prove of great assistance.

MARCH, 1883.

E. E. S.

HISTORY OF TUBERCULOSIS

CHAPTER I.

PATHOLOGICAL ANATOMY AND HISTOLOGY.

*Franciscus Deleboë Sylvius*¹ was the first writer who accurately described tubercles of the lung. Even at that early day, it was known to him that the center of these tubercles might soften or degenerate, and in this way give rise to cavities. It is not at all improbable that *Sylvius* knew of the existence of miliary tubercles also, since he speaks of "tubercula minora." He regarded tubercles as *enlarged scrofulous bronchial glands*; and here we have, for the first time, the intimate connection between phthisis and scrofulosis hinted at.

There is no doubt, that *Manget*² observed miliary tubercles, for he compared them to millet seed, "semen milii." *Manget* made one step in advance, also, and recognized the fact of a general dissemination of these miliary tubercles throughout the body. He, like *Sylvius*, regarded the formation of cavities

¹ Fr. Del. Sylvii, *Medicinae Practicae*, etc. Avenione, 1680. (Waldenburg.)

² Th. Bonnetti Sepulchretum. Joh. Jac. Mëngetus. Genevæ, 1700. (Waldenburg.)

as a result of softened and degenerated tubercles, and vigorously opposed the old teaching, that phthisis and *ulcus pulmonum* were one and the same thing.

The discovery of a general miliary tuberculosis was afterwards completely lost, and so remained until one hundred years had passed, when it was again brought to light.

The teaching of *Sylvius* was then corroborated by the theories of *Morton*,¹ who regarded tubercles as a constant, never-failing, premonitory stage of phthisis pulmonis. But this assumption, also, soon fell into oblivion, and was totally forgotten.

*Morgagni*² agreed, in the principal points, with the views of *Sylvius*, but held that the origin of phthisis solely from softened and broken-down tubercles had not been proved. He maintained also that the accepted view, that tubercles were enlarged glands, was not sufficiently well grounded. *Stark*,³ *Reid*,⁴ and *Cullen*,⁵ soon after agreed with these views of *Morgagni*.

¹ Phthisiologie. Translated from the Latin. Helmstedt, 1780.

² De Sedibus et Causis Morborum. Lipsiae, 1827. II. (Waldenburg.)

³ Med. Communic. 1785. (Waldenburg.)

⁴ An Essay on the Nature of Phthisis. London, 1785. (Waldenburg.)

⁵ Anfangsgründe der Arzneikunst (German Translated.) (Waldenburg.)

A step in advance was made by *Baillie*,¹ by the discovery that the larger tuberculous nodules found in the lungs, to which, for a long time, an effort had been made to accord a place and significance different from that of miliary tubercles, were formed by the confluence of the latter. The characteristic feature of tubercles is, according to *Baillie*, neither their size, nor their location, but the *physical properties of the substance of the tubercles themselves*. This substance *Baillie* terms "*scrofulous matter*," comparing it to fresh cheese, as did *Kortum*² before him, and hence describes it as "*cheesy*." *Baillie* found, too, that this scrofulous matter was not always in the form of small nodules, but might also show itself as an infiltration. *Portal*³ afterwards replaced the name "*scrofulous matter*" by the term, "*tuberculous substance*."

The introduction into medical language of the limiting terms "*scrofulous*," "*cheesy*," and "*tuberculous*," has exerted a marked influence on the progress and development of the views and theories regarding tuberculosis. Thus, by some authors, scrofulosis was identified with tuberculosis, simply because a *cheesy* product was present. Again, there were certain lung

¹ Matthew Baillie. Translated from the English by Soemmering. Berlin, 1794. (Waldenburg.)

² Commenterius de Vitio Scrofuloso. Lemgoviae, 1789. (Waldenburg.)

³ Observations sur la Nature de la Phthisie Pulmonaire, 1799. (Waldenburg.)

troubles, which did not give rise to nodules, but only to cheesy looking alterations, which were regarded as tubercles; ~~while true tubercles,~~ so long as they did not show cheesy degeneration, were regarded as tuberculous products.

In contrast with these researches we find the investigations of *Vetter*.¹ Based on a number of observations, he revived the views of *Morgagni*, that all cavities were not produced by one and the same process. He made a close distinction between the production of cavities in consequence of a suppurative inflammation—having its type in the *ulcus pulmonum* of the older authors—and the formation of cavities by the degeneration of tubercles. He pointed out, furthermore, that we could arrive at no conclusion regarding the similarity and identity of the pathological products of tuberculosis and scrofulosis, based simply upon the cheesy nature of both. He proposed, therefore, to denominate only the substance forming the tubercles as “cheesy,” or “cheese-like,” and to drop entirely from nomenclature the terms “scrofulous” and “tuberculous substances.”

Further on, it will be seen that the views of *Vetter* have gained many adherents in later days.

Vetter, however, in his observations, erred in one particular. He denied any connection between the tubercles of the abdominal organs and those of the

¹ Aphorismen aus der Patholog. Anatomie. Wien, 1803.

lungs, and held that tuberculosis of the lungs and general tuberculosis were two distinct pathological processes.

An astonishing change was inaugurated by the investigations of *Bayle*.¹ He was the first who confidently announced that tuberculosis was not a local process, limited only to the lungs, but was a general disease involving the whole body, which developed itself on account of a tuberculous diathesis.

To him belongs the great merit of being the first to describe the different stages which tuberculous matter undergoes, and to point out that these metamorphoses are characteristic of tubercles. In the beginning, he says, tubercles are hard, translucent, and of a grayish color; later, they become soft, cheesy, and opaque—assuming at the same time a yellow color—until finally they are entirely liquefied by supuration. *Bayle* was also the discoverer of tubercles of the larynx and trachea. It was he, too, who introduced the term “tubercle milare” into pathology.

The views of *Bayle* were still more expanded by *Laennec*.² *Laennec* proved that tuberculosis, in the first stage of its development, generally showed itself in the form of a miliary tuberculosis. *Laennec* taught, furthermore, that there was only *one* kind of cavity

¹ Recherches sur la Phthisie. Paris, 1810. Journal de Méd., Chir., etc., VI., IX. (Waldenburg.)

² De l'Auscultation. Paris, 1819. 2d Edition 1826. Translation of Lud. Meissner. Leipsic, 1832. (Waldenburg.)

formation, namely, that produced by the softening and degeneration of tubercles.

This view had already been expressed, as seen above, by *Manget* and *Morton*, without, however, receiving recognition from their contemporaries. This theory of *Laennec's*, supported by numerous observations, may be regarded as almost undisputed to-day.

Laennec agreed with *Baillie* as regards scrofulosis. Since the pathological products of both tuberculosis and scrofulosis were of a cheesy nature, he saw in them the same diseased process; and, on this account, he regarded scrofulosis as a tuberculosis of the lymphatic glands.

Laennec found in *Broussais*¹ a bitter opponent to his views. Contrary to *Bayle* and *Laennec*, who denied any inflammatory process in tuberculosis, *Broussais* declared phthisis to be a chronic pneumonia,—that tubercles were not neoplasms, but the product of inflammation, and that, too, an inflammatory infiltration into the *parenchyma* of the lungs.

In this controversy between *Laennec* and *Broussais*, we find the first intimation of the division of opinion which was to prevail later, in which tubercles were regarded, on the one side, as neoplasms, and the theory of tubercular infiltration—a result of inflammation—was taught on the other.

¹ Examen des doctrines medicales, 1816. 2d edition, 1821, Paris.—Historie des phlegmasies, 1808. 2d edition, 1816, Paris, (Waldenburg.)

But a still more bitter and dangerous opponent to the *Bayle-Laennec* theory was *Andral*¹. *Andral* had observed that pus, at first liquid, was changed by inspissation into a yellowish cheesy substance; and, from this observation, he declared every cheesy substance, including tubercles, a product of inflammation.

Important as *Andral's* discovery of the cheesy metamorphosis of pus was, nevertheless, his deductions concerning the origin of tubercles were not tenable. His views, also, regarding the characteristic metamorphosis of tuberculous matter, so often noted by *Bayle* and *Laennec*, are opposed, diametrically, to the observations of these latter investigators; for, while they maintained that tubercles were at first of a semi-solid consistency and later became fluid, *Andral* argued from the caseation of pus, that tubercles were primarily fluid, and gradually became more firm and cheese-like.

The theory of *Bayle* and *Laennec*, however, in spite of all opposition, gained ground constantly, especially in France.

In Germany it engaged the attention of *Schönlein*.² He differed in some points from the above-mentioned observers, and rigorously maintained that scrofulosis and tuberculosis were *not* one,—were not identical processes.

¹ Med. Klinik von G. Andral. Translated by Fliess, 1842.

² Pathologie and Therapie, 1839.

But this teaching of *Schönlein* found no favor in Germany, and the influence of the French school predominated, so that even in the works of *Cannstatt*¹ and the first writings of *Rokitansky*,² tuberculosis and scrofulosis are used as synonymous terms, and the latter is often replaced entirely by the former.

*Engel*³ approached somewhat more nearly to *Schönlein's* standpoint. He made a careful distinction between true tuberculosis and tubercular infiltration. He identified the latter only with scrofulosis. Tubercles themselves he regarded, as did *Cannstatt* and *Rokitansky*, as a product of inflammation. The exudation of tubercular inflammations, he says, is distinguished from other inflammatory products only by its small quantity of water, the exudation assuming on this account a cheesy state.

The great importance attaching to these caseous substances in the pathology of tuberculosis and scrofulosis, led to a series of chemical investigations, mainly confined to the substance of tubercles, without leading, however, to any profitable results. *Preuss*⁴ stated that tubercles consisted mainly of caseine. This assertion, however, was proved to be erroneous by

¹ *Specielle Pathologie und Therapie*, Erlangen, 1843.

² *Handbuch der Allgem. u. Spec. Patholog. Anatomie*.

³ *Zeitschrift der Gesellschaft der Aerzte* 1, Heft. 5, Prag, 1845.

⁴ *Tuberculorum pulmonis analysis chemica*, 1835. (Waldenburg.)

T. Vogel.¹ The theory that the substance was a combination of proteines was then generally accepted. Further examinations into the chemical nature of tubercles furnished but meagre results.

Of much more benefit and use to science have proved the microscopical examinations first instituted by *Addison*.² He was the first observer who made a minute and exact microscopical examination of tubercles. He regarded tubercles as a collection of epithelial cells. These cells, he said, originated from the white blood corpuscles which are arrested in the small capillaries, where they undergo a change into epithelial cells.

From his time on, histological examinations of tubercles were diligently followed up, especially after the difficulties of discovering the genesis of tuberculosis and scrofulosis with the naked eye were recognized.

*Lebert*³ soon came to the front with a most important assertion. He maintained that he had found in tubercles peculiar small corpuscles, which were characteristic of tubercles only. He named these peculiar formations "*tubercle-corpuscles*." He was also the discoverer of cancer-cells, which were

¹ Pathol. Anatom. 1, 1845. (Waldenburg.)

² Transactions of the Med. and Surg. Association. Vol. II. (Waldenburg.)

³ Mueller's Archiv. 1844. Traité Practique des Maladies. Paris, 1849.

supposed to be pathognomonic of carcinoma; he therefore emphasized the conclusion that cancer-cells were found only in carcinoma, and tubercle-corpuscles only in tubercles. He, having found these same corpuscles in the products of scrofulosis, therefore maintained that *scrofulous* glands were *tuberculous* glands. But, as an eminent clinician, he could not drop scrofulosis from the category of distinct clinical diseases. He therefore endeavored to find a way out of his dilemma by claiming an identity between tuberculous and scrofulous glands only, and otherwise recognizing scrofulosis in its old form as a distinct and separate diseased process. He likewise declared that form of tuberculosis produced by infiltration of the lung tissue, as of true tubercular origin, on account of the presence of his tubercle-corpuscles.

As a further result of the discovery of tubercle-corpuscles, *Lebert* taught that tubercles were not inflammatory products, but results of a peculiar pathological process.

We will now note what changes and vacillations the doctrine of the existence of specific tubercle-corpuscles has undergone, from the time of *Lebert* to the present day, when the results of the investigations of *Robert Koch* have sent such a thrill of excitement through the whole civilized world.

Strong arguments were soon brought to bear against the views of *Lebert* by *Reinhardt* and *Virchow* in Germany.

Reinhardt,¹ almost simultaneously with *Virchow*,² pointed out that the tubercle-corpuscles of *Lebert* were produced in inspissated pus, from common pus-cells. He showed that through the loss of water and the consequent drying up of pus, its cells shrink, losing their usual configuration, and becoming irregular in outline, and, in this condition, are acted upon but very slightly by acetic acid. These decayed and shrunken pus-cells, he held, were the tubercle-corpuscles of *Lebert*. Tubercles, therefore, were simply deposits of pus, and in no way the products of a distinct pathological process.

It was only a further sequence of the reasonings of *Reinhardt* that he regarded tubercles of a grayish color as a product *sui generis*, since the analogy between tubercles and inspissated pus could have reference only to yellow tubercles; for gray tubercles showed entirely different physical properties. He distinguished, therefore, between gray and yellow tubercles, and denied the change of the one into the other. Both had one thing in common, however, in that each kind was produced by inflammation—the exudation occurring during the development of gray tubercles becoming organized into connective tissue, while the inflammation in the

¹ *Virchow's Archiv*, Bd. I., 1847.

² *Ibidem*.

development of yellow tubercles went on to the development of pus.

Reinhardt deserves great credit for refuting the theory of the specific character of tubercle-corpuscles—a theory which rested on very weak foundations. The theory of a distinct pathological process as regards gray tubercles, was, however, in the light of later investigations, not found tenable.

The pathology of tuberculosis had advanced to this point when *Virchow* began his investigations.

The first matter for which we owe thanks to *Virchow*, was the proof that caseation took place, not only in abscesses, but also in the most various pathological products, as carcinoma, sarcoma, and typhoid ulcerations.¹ For this reason, he did not regard caseation as a distinct pathological process, but saw in it rather a kind of necrosis—a partial, not completed, fatty metamorphosis.

Virchow, also contrary to the views of *Reinhardt*, placed himself on the side of the *Bayle-Laennec* theory, in claiming that the change from gray to yellow tubercles took place.² To him also, belongs the merit of having examined more accurately and thoroughly into the histological structure of tubercles.

¹ *Virchow's Archiv*, I., 1847.

² *Würzburger Verhandlungen*. Bd. I., 1850, Bd. II., 1851. *Die Krankhaften Geschwülste*. Berlin, 1864–1865. Bd. II. *Cellularpathologie*, Berlin, 1859.

Virchow taught that true tuberculosis showed itself in the form of very minute nodules or tubercles, which are built up like granulations, the nodules being composed of round cells of various sizes, with granular contents, the cells being connected together by a delicate net of connective tissue. Sometimes, he remarks, the cells *may become very large, containing at times more than twelve nuclei*. These nodules often contain blood vessels, which are not to be regarded as new productions, but as belonging to the surrounding original tissues. Miliary tubercles, he says, are therefore new heteroplastic formations, and are to be classed under the heading of the lymphomata.

Virchow came to still other deductions by virtue of his histological investigations—deductions, however, which are unwarranted and without proof. Thus, he laid great stress on the point that miliary tubercles were heteroplastic, and not hyperplastic formations of already existing tissues. He drew, therefore, a sharp dividing line between tuberculosis on the one hand, and the whole series of pathological changes following tuberculosis on the other. But this classification was not strictly followed by himself, for he acknowledges¹ that those hyperplasie which he contrasts with tubercles are not always, strictly speaking, true hyperplasie, but are often found combined with heterogeneous elements. He

¹ Die Krankhaften Geschwülste.

acknowledges, too, that in typhoid affections, as well as in leucaemia, new formations of heteroplastic lymphomata may occur. He concedes that defining tubercles as a new formation, has contributed little to the progress of knowledge; for it has only replaced one indefinite and meaningless phrase by another one still more so. *Virchow* leaves us in doubt even as to whether he regards tubercles as inflammatory or non-inflammatory neoplasms, although the great question of the true character of tuberculosis hinged on this very point for a long period.

In the meanwhile, French observers—*Cruveilhier*,¹ *Lorrain*, and *Robin*²—had not been idle; nor had they ceased to regard all cheesy products as of tuberculous origin. Consequently, they pronounced every case of miliary tuberculosis not followed by caseation of tubercles, a distinct disease. They called the small nodules, or tubercles, “*granulations*.” *Empis*³ proposed to call that form of disease which manifested itself by the production of gray tubercles, “*granulie*;” for he, with *Lorrain* and *Robin*, regarded it as a process totally different from tuberculosis. In his views of tuberculosis he agreed somewhat with *Virchow*, teaching that the most various diseased products might undergo caseation. Every

¹ *Traité d'Anatomie Pathologique*. 1862.

² *Compte rendu*, 1854.

³ *De la Granulie*, etc. Paris, 1865.

organism, however, which possessed the capability of leading to caseation, was tuberculous, and therefore, "granulie" might lead to caseation, if complicated with tuberculosis. www.libtool.com.cn

Let us compare for a moment the views of *Virchow* and *Empis*. According to *Virchow*, tuberculosis is a specific disease; while, according to *Empis's* theory, the disease consists really of three distinct processes—granulie, tuberculosis, and granulie combined with tuberculosis. *Virchow* sees in caseation a regressive metamorphosis, while caseation is, according to *Empis*, the tuberculous process itself. Again, *Virchow* regards the development of gray nodules as a fatal disease; *Empis* does not, since granulie is dangerous to life only when complicated with tuberculosis.

The doctrines of *Empis* found adherents in France only, and helped to widen the breach existing at that time between the teachings of the French and German schools. It was only lately that *Cornil* and *Hérard* took up in part the views of *Virchow*.

By the labors of *Niemeyer* and *Buhl* the pathology of tuberculosis was expanded in an entirely new channel.

*Niemeyer*¹ studied especially the relation of phthisis to tuberculosis. According to him, there are *two kinds* of phthisis—the one having its origin in chronic

¹ Vorträge über Lungenschwindsucht. Berl. Klin. Wochensch. 1866 u. 67.

tuberculosis, the other having for its starting point pneumonia—especially in the chronic catarrhal form—which by caseation produces a destruction of lung tissue. ~~Acute miliary tuber~~culosis, he says, is generally but a result of phthisis. As regards scrofulosis, *Niemeyer* agreed with *Virchow* in taking the stand-point that it is a distinct process, related to phthisis only so far as inflammation, in consequence of scrofulosis, may lead to caseation.

*Buhl*¹ some time previous to *Niemeyer's* observations (in 1857), published the results of two hundred and eighty post-mortem examinations, twenty-three of which were cases of acute miliary tuberculosis. He found that in twenty-one out of the twenty-three cases of acute miliary tuberculosis, either cheesy nodules—yellow tubercles—or cavities formed in consequence of these cheesy nodules, were present. From these observations and others to be mentioned later, *Buhl* was led to make the assertion that acute miliary tuberculosis was a specific infectious disease. He argued that a specific virus was present in these cheesy nodules; if this becomes absorbed, minute nodules containing the peculiar poison become disseminated throughout the whole organism. *Buhl* strengthened and supported his arguments by other observations, namely, the topographical relations of the resulting tubercles to the primary infecting centers. He found that, in the beginning

¹ *Zeitschrift für Rationelle Medizin*, 1857.

of the disease, miliary tubercles were to be found only in close proximity to the infecting center; and that, in the later stages, the recently formed miliary tubercles—characterized by their small size, gray color, and soft consistency—were to be sought for in parts remote from the infecting center, while the older tubercles, those of larger size and yellowish color, were situated near the primary center. From these investigations, he came to the conclusion that the production of tubercles is brought about by an infection originating in a primary focus, and which proceeds to develop in a centrifugal manner.

It is evident that the latter conclusions could be accepted as positive evidence, only when the first observation—the constant presence of primary cheesy nodules—was placed beyond all doubt. *Buhl* himself admits, on the one hand, that in many cases of unmistakable acute-miliary tuberculosis, the primary center may be absent; and, on the other hand, that even when the infecting center is present, miliary tuberculosis does not always show itself. This defect in his reasoning he passes over with the remark that, in those cases where the primary center is apparently wanting, it is so minute that it escapes observation, while in the other set of cases where, even with the presence of a cheesy center, miliary tuberculosis does not follow, it is for the reason that the primary nodule is often encased by tough, resistant tissue, so that the

absorption of the cheesy material is impossible. The acceptance, however, of the theory that in those cases where no primary center is observed it is nevertheless present, is liable to mislead, especially, in this connection, where something—the constant presence of a primary center namely—which one was endeavoring to prove, is already taken for granted. The other statement, too, that the tough connective tissue, which surrounds the primary center, prevents the absorption of the virus, and in this way the outbreak of miliary tuberculosis, must also be set down as very arbitrary. It should have been *Buhl's* endeavor to show that the connective tissue, so placed, was actually a barrier sufficient to prevent the absorption of the virus.

Later it was established by post-mortem investigations by those observers, who tested the question as to the constancy of the primary center, that the infection theory of *Buhl* was in no way so well founded as its originator supposed; *Kinkeldeyn*,¹ for example, described ten cases of miliary tuberculosis, in not one case of which, primary cheesy foci were found.

On a footing not much firmer is based the observation of *Buhl* that the primary center is virulent. He neither directly demonstrated the existence of a virus in the cheesy substance, nor indirectly furnished

¹ Beitrage zur Lehre von der Tuberculose. Inaug.-Dissertation. Würzburg, 1868.

satisfactory arguments to support this view. His supposition that the fever occurring during tuberculosis warrants the assertion, that an infection is very probable, can not be accepted as proof of the existence of a virus and its absorption into the system, since the fever and its concomitant symptoms may be brought about by the inflammatory processes, which are always present during the development of tubercles. The assertion, too, that tuberculosis, as a rule, is not found in combination with other infectious diseases, can not be taken as further evidence favoring his theory of infection, when we remember that syphilis and tuberculosis, as distinct and separable diseases, may attack the same individual. *Niemeyer*¹ and *C. E. Hoffmann*² adopted *Buhl's* views, with the distinction, however, that *Niemeyer* expressed himself against the constant occurrence of the primary center, and both opposed the existence of a specific tubercle-virus.

Not long after these first observations *Buhl* again came forward with a series of new investigations. In the year 1856³ *Buhl* had already called the attention of the profession to a new form of pneumonia, the so-called desquamative-pneumonia. In 1872 he published⁴ an extensive and voluminous report, in

¹ Vortraege über Lungenschwindsucht. Berl. Klin. Wochens. 1866 u. 67.

² Deutsches Archiv für Klinische Medizin, IV. 1867.

³ Journal für Rationelle Medizin. 1856.

⁴ Lungenentzündung, Tuberculose u. Lchwindsucht. München. 3 1872.

which he stated that desquamative-pneumonia might appear in two forms: 1st. As a consecutive disease, coming on in the course of acute exanthematous processes; and, 2d. As a genuine desquamative-pneumonia. The last form is not, according to *Buhl*, a local disease, but the "localized expression of a general disease," and it is this affection which is, according to him, the premonitory stage of phthisis pulmonis and tuberculosis.

Buhl again divides the genuine desquamative-pneumonia into two subdivisions: 1. That form which does not lead to caseation; and, 2. That which always ends in caseation. These two forms, according to *Buhl*, differ from each other very imperceptibly, while they stand in marked contrast to catarrhal and croupous pneumonia. *Buhl* himself, however, concedes that both the catarrhal and croupous pneumonia may, at times, lead to caseation.

This concession on *Buhl's* part shows sufficiently, I think, that the differences between croupous and desquamative-pneumonia, so far as the formation of cheesy products is concerned—and it is this which is the all-important factor of *Buhl's* hypothesis—are not so very weighty. From this same point of view, too, objections have frequently been made against his classification.

Caseation is regarded by *Buhl* as a kind of necrosis brought about by an anaemia, due to a compression of the blood-vessels of the lung. He comes to this

conclusion by a series of speculations, and not by univocal observations. This is clearly shown by those deductions of *Buhl* which are based upon the changes going on in the minute capillaries of the lung,—changes which can only be determined by direct observations, which *Buhl* did not make.¹

In these later articles, *Buhl* modifies somewhat his former views concerning the importance of the primary infecting center. He grants that the poison may be the product of general nutritive changes, and that it need not of necessity be collected together at one spot, but may be found distributed over various parts of the body. This acknowledgment of *Buhl* is, however, equivalent to a retraction of his theory of infection. He himself seems to have regarded his theory as based upon rather unstable foundations, since he gives his sanction to *Waldenburg's* observations, who declared that tuberculosis might follow in the course of diabetes and the chronic exanthemata, without being preceded by the formation of cheesy foci.

We can not, therefore, lay much stress upon the further endeavors of *Buhl*, who tried, notwithstanding these facts, to sustain his theory of the infectiousness of tuberculosis by vague speculations and experimental evidence. It may not be out of place to mention in this connection that *Buhl* was inclined to consider his experiments by inoculation as of more importance than his anatomical-pathological investi-

¹ *Zeitschrift für Rationelle Medizin*, 1857, pp. 72, 77, 78.

gations. The results of his inoculation experiments will be treated in that connection, in the chapter especially devoted to that subject.

The views of *Buhl* were bitterly opposed by *Heitzmann*.¹ He, from observations in two hundred post-mortems of persons dying from phthisis, came to the conclusion that tubercles, as well as tuberculous infiltration, were inflammatory neoplasms without the formation of new blood-vessels, and that, on account of the want of blood-supply, the neoplasms underwent changes, resulting in caseation. With these views, he opposed the doctrines of *Virchow* as well as those of *Buhl*, and even asserted that the teachings of *Virchow* rest in part on presumptive evidence.

Virchow considered, as has already been mentioned, the so-called scrofulosis of the lymphatic glands as *hyperplasiae*, leading to caseation, and tubercles as *heteroplasiae*, likewise undergoing cheesy metamorphosis.

Heitzmann showed by examinations of tuberculous and scrofulous lymphatic glands, that very often not a single anatomical characteristic could be found by which the two might be distinguished from each other.

Against *Buhl's* hypothesis of infection, *Heitzmann* pointed out that miliary tuberculosis could not be dependent on pre-existing cheesy centers, since *Buhl*

¹ Ueber Tuberkelbildung; Mediz. Jahrbücher. 1874.

himself found no infecting center in ten per cent of the cases coming under his observation. According to *Heitzmann*, no perceptible service had, at the time he wrote, been rendered to a knowledge of the pathological anatomy of tuberculosis, the main effort having been, seemingly, to eliminate the errors from *Buhl's* doctrines and to harmonize anatomical observations with them. The great problem, however,—the question as to the nature of tuberculosis—remained, as before, in total darkness. In this state of affairs, it is not to be wondered at that it became customary, in many places, to make no post-mortem examination of persons dying from phthisis.¹

The study of the pathological histology of such cases was, on the other hand, the more diligently pursued; and, in order to gain a thorough understanding of these histological examinations, we must again retrace our steps to a somewhat earlier period.

In the year 1866, an article appeared by *E. Wagner*,² in which he described tubercles as consisting of two distinct elements, the one being a network of ramifying tissue fibrillae, and the other the cells contained in the meshes of this network. Neither of these observations, however, presented any thing new, for *Virchow* had already described these very same condi-

¹ Volkmann's Vortraege, No. 30. Ueber den Gegenwärtigen Stand der Tuberculosenfrage. Ruhle.

² Archiv für Heilkunde. 1866.

tions. The only new observation was that tubercles were nodules of a reticulated or adenoid substance.

Shortly afterward, *Langhans*¹ called attention to the presence of large, irregular cells in tubercles, and although *Virchow* had discovered them some time before, they were given the name of "*Langhan's* giant-cells." The numerous nuclei of these cell are, according to *Langhans*, generally situated near their margins; he also observed that these giant-cells may be found in tubercles occurring in almost all the tissues of the human body, except in those of the pia-mater.

More accurate statements concerning the histogenesis of tubercles are made by *Knauff*.² His observations have reference to miliary tubercles of the serous membranes. He described tubercles as circumscribed collections of embryonic cells, which afterward become organized into connective tissue. The matrix of these embryonic cells, he thinks, is found in the small lymphatic elements scattered throughout the serous membranes. He, furthermore, pointed out that blood-vessels might be wanting entirely.

*Klebs*³ made his examinations in the same direc-

¹ Virchow's Archiv. Bd. 42.

² Zur Histologie der Miliartuberculose. Med. Centralblatt, 1867. M. 36.

³ Beitrage zur Geschichte der Tuberculose. Virchow's Archiv. 44 B. 1868.

tion, and silver preparations of tuberculous serous membranes furnished him appearances which led him to believe that the endothelial cells of the lymphatics took part in the production of miliary nodules; from this he drew far-reaching conclusions as to the propagation of miliary tuberculosis by means of the lymphatics.

Up to this time we find, then, two sources of origin for tubercles conjectured; on the one hand, the lymphatic cells—on the other, the endothelium of the lymph vessels. A third form of genesis was soon after proposed.

*Schüppel*¹ declared that tubercles of the liver were of embolic origin. The vessels of tuberculous livers, says *Schüppel*, contain certain cells similar to the cells of tubercles, which, collecting together, form minute nodules in the lumen of the vessels. He thought, also, that some of his observations pointed to transition stages between tubercle cells and the white corpuscles of the blood—a supposition which *Addison* had already entertained—and supposed that the tubercle cells of these embolic nodules originated directly from the white blood-corpuscles.

The statement of *Schüppel* regarding the formation of tubercles in blood-coagula (thrombi) seemed, indeed, to be in harmony with similar observations

¹ Archiv. der Heilkunde; IX. 1868.

of *Rokitansky*.¹ Little notice was paid, however, to these assertions, and even *Virchow*² directly opposed the supposition that such might be the case. Simultaneously with *Schüppel*, *Bicsiadecki*³—then assistant of *Rokitansky*—published a description of four cases of tuberculosis, in all of which tubercles had formed in the extravasations that had taken place into the serous cavities.

*Schüppel*⁴ did not rest here, but soon after published other articles regarding the development of tubercles in lymphatic glands, in which he presents new observations concerning the genesis of tubercles and giant-cells, which differ entirely from his former statements.

All tubercles, in conformity with these observations, consist at first of giant-cells, originating in the blood- or lymph-vessels. Tubercles, however, do not consist solely of giant-cells; but the tissues surrounding the giant-cells become diseased, and these diseased tissues, together with the giant-cells, constitute the tubercles.

Schüppel describes a tubercle as follows:

“In the center of the tubercle, or very near its center, a giant-cell, with many nuclei, is generally found,

¹ *Lehrbuch der Pathologischen Anatomie*. Bd. I., p. 305.

² *Gesammelte Abhandlungen*, p. 550.

³ *Sitzungsberichte der Wiener Akademie*. Bd. 57. 1868.

⁴ *Untersuchungen über Lymphdrüsen-Tuberculose*. Tübingen, 1871.

surrounded by numerous embryonic elements, similar to those found around epithelial cells. The giant-cells decrease in size from the center to the periphery, until very near the margins of the tubercle they become embryonic cells. These 'epitheloid' cells originate from the lymph-cells of the follicles, while the reticulum is developed either from the old adenoid network or from the walls of the blood-vessels. The regressive metamorphosis which takes place later affects primarily the giant-cell, and in a centrifugal direction approaches more and more the periphery of the tubercle. During the progress of this cheesy degeneration, concretions may be formed in the giant-cells."

At this time, *Cohnheim's* theory of the migration of the white blood-corpuscles had already gained so many adherents that it is to be supposed that *Schüppel* published his observations under the influence of this theory. The direct demonstration, however, that tubercles originated from migrated blood-corpuscles was first given by *Waldenburg*.¹ The doctrine of the migration theory of tuberculosis has always found in this observer one of its warmest supporters.

But opposition to this theory was not wanting long.

*Kundrat*² showed that, in tubercular eritonitis, the

¹L. c.

²Mediz. Jahrbücher. 1871.

endothelium of the peritoneum furnishes the matrix for the proliferations. *Hering*¹ made similar observations, and added to *Kundrat's* views by making the tubercles originate directly from the endothelial cells.

From this time on, the theory of the development of tubercles from migrated cells, gradually fell into oblivion, and it is only within the last few years that *Martin*² again endeavored to revive it.

Through the investigations of *Schüppel*, the histological aspect of our question has received an impulse in a direction similar to the one which the observations of *Lebert* gave to it. As *Lebert* had taught that every tuberculous product contained tubercle-corporuscles, so at this time the idea became prevalent that every pathological product that contained giant-cells was of tuberculous origin. In consequence of this idea, *Schüppel*,³ in his further examinations, declared the nodules which develop themselves in the course of the cattle plague (murrain) to be true tubercles.

The supposed identity of murrain with tuberculosis occurring in man had led, before, to much discussion, and the discussions became the more interesting when the inoculation of matter from pearl-nodules (murrain) proved operative.

¹ Histolog. u Experiment. Studien über die Tuberculose. Berlin, 1873.

² Med. Centralblatt, 1880. No. 42.

³ Schüppel, Ueber die Identität der Tuberculose mit der Perlsucht. Virchow's Archiv. Bd. 56. 1872.

Originally, pathologists were of the opinion that murrain, although nodules were present, was a different pathological process from tuberculosis, because the anatomical conditions were in many instances widely different. Tuberculosis has its starting point generally in the lungs; murrain in the serous membranes. In tuberculosis we find miliary nodules, while those present in murrain vary in size from a pea to a child's head. Tubercles again generally undergo caseous, pearl-nodules calcareous, degeneration. The histological examinations of *Virchow* have furthermore shown that the pearl-nodules resemble more the type of sarcomata. The observation, however, that inoculations with material derived from pearl-nodules would produce nodules in various parts of the inoculated animal, induced pathologists to resume again the discussion of the identity of tuberculosis and murrain.

In this discussion, *Schüppel* now maintained that pearl-nodules were histologically exactly similar to tubercles; and that murrain and tuberculosis were, therefore, one and the same disease. This assertion, however, was soon disputed. *Kolesnikow*¹ found the nodules occurring in the mammary glands of cows suffering with murrain, not formed like tubercles, but approaching more the character of lympho-sarcoma. These investigations of *Kolesnikow*

Die Histologie der Milchdrüse. Virchows, Archiv. Bd. 70. 1877.

were however, entirely disregarded, and received no recognition, observers plodding away in the path which *Schüppel* had laid out for them.

*Friedländer*¹ went still farther in this direction and declared that lupus, too, from its histological structure, was a localized tuberculosis, because the presence of giant-cells was recognized. He also found giant-cells in the stroma of carcinoma and in ulcus rodens. All these he regards as localized tuberculoses.

Soon after this publication by *Friedländer*, *Köster*² announced that he had seen giant-cells in chancre on the nose, in a syphilitic looking ulcer on the penis, in a case of elephantiasis of the labium, in granulation tissue of caries of bone, in abscess of the mamma, and in an iris granuloma; and, basing his conclusions on these observations, *Köster* declared that all these various diseased processes must be regarded as of tuberculous origin.

This view was strengthened by a publication by *Griffini*³ on lichen syphiliticus. This observer, in his examinations of diseased skin, continually detected giant-cells, and therefore concluded that this affection, too, was of tubercular origin.

Side by side with these investigations, numerous

¹ Beitrage zur Kennsniss des Lupus, U. S. V. Med. Centralblatt, 1872, No. 43.—Virchow's Archiv. Bd. 60, 1874, and Volkmann's Samml. Klin. Vortraege, No. 64.

² Mediz. Centralblatt, 1873, No. 58.

³ Mediz. Centralblatt, 1875.

other observations and publications found their way before the profession, in all of which the theory of a "localized tuberculosis" resting on histological foundations was vigorously opposed. These investigators pointed out that giant-cells were developed in the most widely different diseases, diseases that had nothing in common with tuberculosis. I will mention a few only of the most prominent of these observers.

*Steudner*¹ showed that giant-cells are often found in sarcoma, not connected with tuberculosis in any way. Almost at the same time, *Milani*² observed giant-cells in sarcoma of the lymphatic glands, and for these reasons denied the specific character of giant-cells.

*Jacobson*³ showed that in wounds with a good granulating surface, giant-cells, exactly like those found in tuberculous products, sometimes develop.

Furthermore, observations were made by *Th. Herring*⁴ that tubercles possess no specific structure, since some of the so-called specific constituents are often entirely wanting. He indeed demonstrated that in certain tubercles, *Langhan's* giant-cells are never found. He declared that tubercles which develop on the surface of serous membranes are des-

¹ Virchow's Archiv. Bd. 59, 1871.

² Medizin. Centralblatt, 1871, No. 39.

³ Virchow's Archiv. Bd. 65, 1875.

⁴ Histologie und Experim. Studien über die Tuberculose. Berlin, 1873.

titute of giant-cells, while tubercles which flourish in inflamed tissues usually have a reticulum with giant-cells. www.libtool.com.cn

*Bizzozero*¹ found giant-cells in syphilitic ulcers of the skin; *Brodowski*² in a case of disease of the muscles of the heart; *Rindfleisch*³ in syphilitic nodules of the liver; *Unna*⁴ in hard chancre; and *Heubner*⁵ in syphilitic changes of arteries of the brain. Lastly, *P. Baumgarten* has completely overthrown the theory of the specific character of giant-cells, by a series of accurate and thorough investigations. It will not be out of place in this connection, however, to notice the investigations of *Ziegler*. *Ziegler* introduced two small glass plates, separated only by a capillary space, underneath the skins of various animals, and was able to observe between the plates, after the lapse of a certain time, the appearance of giant-cells,⁶ and the collection of small, round cells,⁷ which he regarded as tubercles. These investigations, however, do not allow of positive deductions regarding the development of tubercular nodules. For what

¹ *Mediz. Centralblat*, 1873, No. 19.

² *Virchow's Archiv*. Bd. 68, 1876.

³ *Lehrbuch der Patholog. Gewebelehre*.

⁴ *Vierteljahrsschrift für Dermatologie*, 1878.

⁵ *Luetische Erkankung*. Leipzig, 1874.

⁶ *Experimentelle Erzeugung von Riesenzellen*. *Med. Centralblatt*, 1874, No. 58.

⁷ *Untersuchungen über Pathologische Bindegewebs und Gefässneubildung*. Würzburg, 1876.

warrant was there for coming to the conclusion that the development of collections of cells between two plates of glass was analogous to that of tubercles? This much can only be said of the value of *Ziegler's* investigations, viz: that giant-cells can be produced experimentally in non-tubercular animals.

Such was the situation when *Baumgarten*¹ began his investigations. He also produced giant-cells experimentally in non-tubercular animals, not, however, between glass plates, but in granulations themselves. He demonstrated that granulation tissue is constantly formed around ligatures of blood-vessels, in which tissue, giant- and epitheloid-cells are found. Almost at the same time *Giovanni Weiss*² made similar observations, by introducing hairs and cotton fibers under the skins of dogs and pigeons.

*Baumgarten*³ showed, furthermore, that when foreign bodies of almost microscopical dimensions (hairs, particles of dust and dirt, etc.) were implanted in subcutaneous connective tissue, giant-cells might be artificially produced, and indeed typical tubercle giant-cells, with a peculiar position of their nuclei. These giant-cells are found either scattered in the newly-formed tissues or in the center of the nodules, like collections of epitheloid-cells, which are situated

¹ *Medicin. Centralblatt*, 1876, No. 45.

² *Virchow's Archiv*. Bd. 68, 1876. Ueber die Bildung u Bedeutung der Riesenzellen.

³ *Zur Tuberculosenfrage*. *Med. Centralblatt*, 1878, No. 13.

in the meshes of an adenoid network. Very often the giant-cells contain particles of the introduced foreign bodies in their interior. *Baumgarten* has compared sections of such nodules, with preparations of miliary tuberculosis, and was not able to find any marked or noteworthy difference between the two. He comes to the conclusion, founded on these investigations, that miliary tuberculosis can be developed by artificially-produced inflammation, and that, for this reason, the "giant-cell tubercle" was not a characteristic product of miliary tuberculosis.

It was further demonstrated by *Baumgarten* that those syphilomata, which appear in the form of miliary nodules, have exactly the same structure as miliary tubercles, and that they may even undergo caseation from the center outwards. He found nodules of the same structure also in an osteo-sarcoma of the tibia.¹ All these observations *Baumgarten* considers important links in a chain of evidence against the acceptance of the theories of a localized tuberculosis, the identity of lupus with tuberculosis and of murrain with tuberculosis. The experiments of *Baumgarten* pointed, moreover, to the conclusion that tubercles produced by inoculation must, from an histological standpoint at least, be regarded as products of inflammation—an inflammation in conformity with the

¹ Uber ein Knochensarcom. Virchow's Archiv. Bd. 76. 1879.

microscopic character of the irritant, attacking, at the outset, only minute microscopical parts of the animal tissues.

In a later publication, *Baumgarten*¹ finally called attention to the clinical peculiarities of lupus and of tuberculosis, and declared the identification of these two processes as one and the same, as unscientific and invalid.

These weighty arguments have completely overthrown the theory of the specific character of giant-cells, although *Volkman*² made one more effort to establish it.

With the decline of this doctrine, the theory that local tuberculosis is a diseased process with distinct histological features, also fell to the ground. *Cohnheim* disputed this theory, and in its place substituted an hypothesis of his own, which was not at all tenable. He claimed that tubercles can not be defined anatomically. The greatest variety of nodules, from tubercles to the products of lupus, equinia, and syphilis, form properly a distinct and peculiar group of pathological products; these he denominated as "infection tumors;" but he has failed to prove satisfactorily that all these tumors which he names, and especially tubercles and lupus-nodules in man, are in reality *infection* tumors.

¹Über Lupus und Tuberculose. Virchow's Archiv., 1880, Bd. 82.

²Lupus und Tuberculose. Berliner Klin. Wochenschrift, 1875.

This hypothesis of *Cohnheim's*, however, contrasts sharply with the results of the investigations of *Baumgarten* and *Ziegler*. For, according to *Cohnheim's* interpretation, the miliary inflammatory centers produced by these observers, experimentally, would have to be regarded as infection tumors—a conclusion, for which there is not a single plausible reason.

The other remark of *Cohnheim's* that tubercles, from an histological standpoint, can not be defined, accords in fact—as far as it concerns tubercles of a low stage of development—with the present state of the histology of tubercles. The more recent histological investigations, especially the work done by *Gaule*¹ and *Tul. Arnold*,² have indeed furnished us with many histological details, but the question as to the nature and origin of tuberculosis has not been brought much nearer to a solution. These investigations, however, have reduced the formerly generally acknowledged and apparently fundamental differences between tubercular and inflammatory products, to such minute and unimportant proportions, that, at the present time, a trustworthy diagnosis, discriminating between the two pathological products, is hardly possible.

This fact makes it clear why both anatomists and histologists, appeal, not only in order to prove the infectiousness of tuberculosis, but also in regard to

¹ Virchow's Archiv. Bd. 69. 1877.

² Virchow's Archiv. Bd. 82, 83, 88.

differential diagnosis, to the evidence derived from experiments upon animals.

Let us now, in a few lines, take a view of the situation: The microscope has revealed the character of miliary tubercles. It has demonstrated a cellular structure, an intercellular net-work, and often, but not always, the presence of giant-cells. Not one of these elements has, however, in and of itself, proved to be a characteristic of true tubercles, although it must be conceded that we may, *with all these three elements combined, and by paying attention to the regressive metamorphoses*, be able, under certain conditions, to make at least the histological diagnosis of tubercles.

Tubercles, however, in low stages of development, that have not as yet the above-mentioned elements incorporated within them, are beyond the range of successful examination and elude a positive microscopical diagnosis.

So far, then, histological and pathological anatomical investigations have thrown no light upon the nature of tuberculosis or upon its causes, although we must not forget that the morphology of tubercles has advanced as far as the present state of histology will permit.

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CHAPTER II.

INOCULATION EXPERIMENTS.

The first effort to produce tuberculosis artificially dates back, as far as known, to the year 1789. At this time tuberculosis and scrofulosis were regarded by anatomists as one and the same disease. *Kortum*¹ inoculated a boy in the region of the neck with "scrofulous pus." The result, however, was negative.

Similar experiments were made some time after by *Hébréard*² on dogs, and by *Lepelletier*³ on guinea-pigs, with like negative results. *Lepelletier*,³ *Goodlaad*,⁴ and *Deygallières*⁴ even went so far as to inoculate themselves, without, however, producing tuberculosis.

The first successful inoculation with true tuberculous matter was accidental.

*Laennec*⁵ wounded himself in the index-finger with

¹ *Commentarius de Vitio Scrophuloso.* 1789. (Waldenburg.)

² *Essai Sur les Tumeurs Scrofuleuses.* Thèse Inaug. Paris, 1802. (Waldenburg.)

³ *Traité Complet de la Maladie Scrofuleuse.* Paris, 1830. (Waldenburg.)

⁴ *Théorie Nouvelle de la Maladie Scrofuleuse.* Paris, 1829. (Waldenburg.)

⁵ *Abhandlungen von den Krankheiten der Lungen.* Leipzig, 1832.

a saw, while making a post-mortem examination of a body affected with tuberculosis. A minute round nodule developed in the wound, without being followed, however, by symptoms of a general infection. *Laennec* died from tuberculosis, a quarter of a century after this accidental infection. It certainly would not be reasonable to attribute the death of *Laennec*, after this long lapse of time, to this wound received so many years before.

Albert,¹ somewhat later, published five cases of accidental inoculation with tuberculous matter occurring during the examination of diseased lungs, in none of which cases was tuberculosis afterward developed.

None of these observations favored the theory of the contagiousness of scrofulosis and tuberculosis.

Other experiments were, at the same time, being prosecuted by observers, who upheld the opinion that tuberculosis might be an inflammatory process.

The first investigators who experimented in this direction were *Gaspard*,² in 1812, *Lombard*,³ and *Barignan*.⁴

Systematic experiments, however, were first undertaken by *Cruveilhier* in 1826.⁵ He injected mercury

¹ Rust's Magazin, 1834.

² M. Cruveilhier's *Traité d'Anatomie Pathologique*, 1826, p. 704., Bd. IV.

³ Virchow's *Geschwülste*, Bd. II.

⁴ Waldenburg, *Tuberculose*, p. 186.

⁵ Cruveilhier's *Traité d'Anatomie Pathologique*, Bd. IV., 1836.

into the trachea and into the veins, and observed as a result numerous nodules in the lungs, the liver, and the mesentery. The tubercles often contained in their centers one or more very minute particles of mercury, surrounded by a cheesy pus. *Cruveilhier* came to the conclusion, from these experiments, that tubercles are not specific pathological products. He claimed that the formation of tubercles is an inflammatory process, which does not, however, develop ordinary pus, but a cheesy product of some kind.

We encounter here, for the first time, the acceptance of an insufficiently well-founded theory, the defects of which have not been eliminated up to the present day, and have produced no little confusion in the discussion of tuberculosis. It is of sufficient importance to claim special attention here.

No one who has read *Cruveilhier's* description of his experiments and the resulting nodules, will doubt for a moment that the nodules were produced by the mercury injections, and that they were very similar to tubercles of the human subject. But it is an entirely different question as to whether these nodules, produced by injections of mercury, are really *identical* with human tubercles.

Cruveilhier thought that he was justified in deciding that they were, both on account of the anatomical similarity of the nodules to tubercles, and because of the resulting marasmus and consequent death of the animals experimented upon.

Almost all the subsequent experimenters have followed *Cruveilhier* in this regard, and have declared the nodules following inoculation to be true tubercles, no matter whether tuberculous or non-tuberculous matter had been used for the experiments.

But there are objections to the view of regarding nodules produced in animals by inoculation as true tubercles; for the whole clinical and anatomical aspect of tuberculosis is not completed simply by the production and appearance of nodules and consequent inanition. In order to interpret correctly all the clinical features, and to prove indisputably the identity of the artificially produced nodules with human tubercles, the appearance of fever and hæmoptysis, the history of the development and regressive metamorphoses of tubercles, the production of cavities, and the amyloid degeneration of the abdominal organs, should also have claimed the attention of the observers, and, if possible, should have been put beyond all doubt and dispute.

Cruveilhier's conclusion would seem to be rather a daring presumption. Very many products of disease appear in the form of nodules, and almost every serious disease leads, as a rule, to marasmus, especially in the case of animals poorly fed and cared for, like those experimented upon.

Cruveilhier's experiments teach us only that mercury injections may, at times, produce a fatal disease in dogs; but they do not prove, that this

disease is one and the same with tuberculosis in man.

*Richard Vines*¹ made similar experiments. He injected blue vitriol, blood from rabid dogs, and irritating liquids into the veins and tracheæ of perfectly healthy mules, and was able, on post-mortem examination, to demonstrate nodules—sometimes in the lungs, and at others in the Schneiderian mucous membrane and in the skin.

Since *Vines* met with the same results after injections of matter which he had taken from horses suffering with malleus, he made the assertion, that not only inoculations with the matter from malleus, but inoculations with irritating substances generally would produce equinia.

Vines fell into the same error as did *Cruveilhier* before him; for, just as the latter failed to demonstrate that the clinical disease produced by him was tuberculosis, so *Vines* did not prove, that the disease which he produced was actually equinia.²

Vines might more properly have formulated his conclusion in such a manner as to say, Inoculations with irritating substances may produce in mules a disease characterized by nodules.

It must be mentioned here that *Vines* held that a

¹ Richard Vines, *Praktische Abhandlungen*, etc.

² *Vines* might easily have proved, that he was dealing with equinia, if he had shown that healthy animals became infected on living in the same quarters with the animals inoculated.

predisposition was necessary in order to produce these nodules; for, in many cases, his inoculation experiments on animals were not successful and yielded only negative results.

The experiments of *Vines* were successfully repeated by *Erdt*.¹ He inoculated horses with scrofulous pus from human subjects, and observed a production of nodules in the animals, and a manifestation of disease which followed. This disease, he pronounced equinia; and, on account of the matter used in experimenting, he held that scrofulosis and equinia were identical diseases.

Renault and *Bonley*² both made injections with ordinary pus into the veins of horses, arriving at results, which they thought to be in conformity with the theory of *Vines*.

Careful and discriminating study of the descriptions given by these experimenters of the nodules produced by them, as results of inoculation, makes it appear very probable, that all these various nodules had one and the same pathological significance. Since these same nodular products were regarded by some experimenters as tubercles, by others as malleus nodules, and again by still others as scrofulous nodules, nothing is proved, more than that each observer judged the results of his experiments

¹ Die Rotzdyscrasie, etc., Leipzig, 1863.

² Recueil de méd. vétér, 1840. (Waldenburg.)

rather according to his own individual inclinations, than according to a standard logical principle. The probable force of individual bias on the part of these observers is more readily realized, when we note that later observers, apparently with no knowledge of the doings of their predecessors, have made similar experimental investigations, and, notwithstanding the warnings they might have found in the literature of the subject, have erred in the same way.

If we consider, then, the actual results of these experiments, we see that not only ordinary and scrofulous pus, but also indifferent substances introduced by inoculation into the organisms of animals, lead to the formation of nodules.

The first experimenter, who purposely and successfully produced infection by the inoculation of tuberculous matter, seems really to have been *Sevell*.¹ He made several experiments, by inoculating matter derived from tubercles of the lungs of horses. The results, however, could not, without further investigation, be made of use in determining the pathology of tuberculosis of man, since it could not be ascertained with any degree of certainty, that tuberculosis of the horse was identical with that of man.

¹ From Vines's *Abhandlungen*.

²*Sevell* came to the conclusion, from the results of his experiments, that pus from tubercles just as surely produced tubercles as that one potato produces another.

In the year 1843, *Klencke*¹ first made the public announcement that, after the inoculation of rabbits with miliary tubercles and infiltrated tuberculous matter, the animals became tuberculous, and that this tuberculosis preferably manifested itself in the lungs and the liver. It must, therefore, be regarded as a mistake to accord to *Villemin* the distinction of being the discoverer of the inoculability of human tuberculosis. *Villemin*'s first publication that tuberculosis was inoculable appeared twenty-five years after *Klencke*'s investigations. *Waldenburg*² called attention to this; but, notwithstanding these facts, *Villemin* is still, almost universally, regarded as the discoverer of tuberculosis by inoculation.

Whether the disease produced by *Klencke*, was actually identical with tubercülosis of man, must, as in the investigations of *Cruveilhier*, still be considered an open question. This much only can be said, that the nodules resulting from his inoculations were, clinically and anatomically, of the same value, only as those of *Cruveilhier*, *Vines*, and other experimenters. *Klencke*, therefore, has only demonstrated—and thereby advanced a step—that, just as the introduction into the system of pus, mercury, and other substances, was followed by the appearance of nodules in various organs of the body, so inoculation with

¹L. c.

²Untersuch ngen und Erfahrungen, etc., von Prof. Klencke. Leipzig, 1843. Bd. I.

tuberculous products from the human dead body was followed by the same results.

The next question which now began to occupy the thoughts of experimenters, was the *modus* of development of these nodules following inoculation.

Panum,¹ who had produced numerous nodules by injecting wax emulsions into the veins of dogs, and had declared the miliary forms of these nodules identical with miliary tubercles of man, declared that tubercles were of embolic origin.

So far, the experiments detailed above have had very little influence on the progress of the pathology of tuberculosis; for the experiments of *Klencke*, as already mentioned, soon ceased to attract attention, and subsequent investigators did not interest themselves in, or attach much importance to, the study of the inoculation of tuberculous matter. It was only after the investigations of *Villemin*, that the question of the inoculability of tuberculosis was again earnestly discussed.

In the year 1865, *Villemin*² reported to the Academy of Medicine in Paris, that, after subcutaneous inoculations of rabbits with human tuberculous material, disseminated tuberculosis was developed. He declared, therefore, that tuberculosis, like syphilis and malleus, is a virulent disease. Somewhat later

¹ Experimentelle Beiträge zur Lehre Von der Embolie. Virchow's Archiv. Bd. 25, 1862.

² Gazette Méd. de Paris, December, 1865.

(1866 and 1868)¹, *Villemin* repeated his experiments with similar results. He observed also, at times, as a result of inoculation, the production of cavities in the lungs, and of hairless spots covered with scabs, on the surface of the body. He experimented with like success on guinea-pigs. But the carnivora were found to possess great powers of resistance against inoculation, so that, for example, of five dogs inoculated, only one developed tubercles in the lungs, and that after a lapse of five months. *Villemin* affirmed, too, after a series of new investigations, that murrain of cattle was identical with tuberculosis of man.

To prove still more positively the existence of a tubercle-virus, *Villemin* made a number of counter-experiments. He inoculated several animals (twelve rabbits and one dog) with phlegmonous pus, carcinomatous matter, cheesy products of lymphatic glands, particles of false membranes and of inflamed lung, without producing in any case the development of tuberculosis. From these negative results, *Villemin* declared, that tuberculosis was due to a specific virus; and he maintained, furthermore, that this virulence was the only certain criterion of the disease, for the reason that neither the anatomical nor the histological structure sufficiently characterized tubercles.

Villemin had peculiar ideas concerning scrofulosis.

¹ Allg. Med. Central-Zeitung, 1866. Etude sur la Tuberculose. Paris, 1868.

His inoculations with scrofulous matter were followed in some cases by positive and in others by negative results. He therefore regarded scrofulosis in some cases as tuberculosis, and in others, also, as simple scrofulosis. Even prior to this time pathologists had endeavored to prove or disprove the hypothesis that scrofulosis was a modification of tuberculosis; but, during all this time, however, scrofulosis had always been regarded as a pathological unity. *Villemin*, however, opposed this view, and affirmed that that which was formerly called scrofulosis, was in some cases scrofulosis and in others tuberculosis.

Villemin's views gained almost universal sanction, for the reason, it seems, that his assertions were supported by counter-experiments, and his method of subcutaneous inoculations could be practiced without any difficulty; his experiments were soon corroborated by a number of investigators. Notwithstanding all this, his labors and conclusions are not fully satisfactory; not, however, on account of anything brought to light by subsequent investigations, but for reasons which must become apparent after an unbiased and impartial consideration of the discoveries of his predecessors. For, opposed to the counter-experiments of *Villemin*, stand the investigations of *Cruveilhier*, *Vines*, *Erdt* and *Panum*, who developed a disease characterized by nodules, by employing various non-tuberculous substances. If *Villemin* was not able to succeed in this, this negative result cer-

tainly can not invalidate the successful attempts of the other experimenters; and this the less, from the fact that his predecessors were obliged to search most carefully for nodules produced by the injection of indifferent substances, before they succeeded in discovering them and were able to publish anything concerning them. They had nothing to lose; no great theory depended upon their results. *Villemin*, on the other hand, may have deemed it desirable to find no nodules in his counter-experiments; for, in that case only was it possible for his alleged great discovery to survive. It may, therefore, be very probable, that he overlooked that which he did not desire to see. Then, too, accidents will occur, and now and then thirteen inoculations with indifferent, perhaps slightly irritating, substances might fail, while in one hundred other cases they would be successful. Besides, it was shown by the investigations of *Villemin's* predecessors that not all animals were affected alike by inoculation, but that nodules developed only in animals with a special predisposition.¹

¹[*Formad* divides animals into two classes—scrofulous and non-scrofulous—according as they show a disposition to the formation of inoculation nodules, or not. He furthermore points out, that this disposition possesses anatomical characteristics—the connective tissue of the scrofulous animals being more abundantly supplied with “round” cells, the lymph spaces being narrower and their number smaller, than of the non-scrofulous animals. Non-scrofulous animals may, by bad food, etc., become

Concerning the experiments of *Villemin* with murrain materials, I have to offer also the following remarks: *Villemin*, as I mentioned above, considered the positive results gained by inoculation of pearl-nodules (murrain), as sufficient proofs, for the assertion, that tuberculosis and murrain were identical diseased processes. This conclusion, however, is not sufficiently warranted, for the results of the inoculation of pearl-nodules are capable of another interpretation. I have mentioned in another place that murrain, in contradistinction to tuberculosis, shows itself by a series of anatomical pathological peculiarities, which characterize it as a diseased process *sui generis*. We might, for this reason, also conclude that non-tuberculous substances are capable of producing tubercle-like nodules, and that, therefore, tuberculosis possesses no distinct virus. In this way, too, we might regard these investigations with pearl-nodules as counter-experiments—which, contrary to the counter-experiments of *Villemin*, have given positive results by inoculation, and thus act unfavorably to the hypothesis of a specific virus. This conclusion, too,

scrofulous. *Formad* refers here to observations made on imprisoned wild animals. The same, however, also holds true as regards dogs and cats, which, in consequence of bad food, acquire a disposition to become tuberculous, after the inoculation with other substances—pulverized glass for instance—and even after traumatic influences. Philadelphia Medical Times, Nov. 18, 1882. E. E. S.]

would have been more in accordance with the literature at that time than the one offered by *Villemin*, viz., that murrain was identical with tuberculosis.

Villemin also advanced new evidence in favor of the identity of inoculation-tubercles with tuberculosis of man. He observed at times a development of cavities in the lungs of the animals inoculated; but this fact certainly loses much force when we remember that *Panum*¹ observed the development of cavities in lungs after inoculation with carcinomatous matter. We are justified, therefore, in coming to one of two conclusions: either inoculations of carcinomatous as well as tuberculous substances may produce tuberculosis, or it is not yet proved, whether or not inoculation with either tuberculous or carcinomatous substances results in the formation of tubercles.

Villemin made a third assertion, also, that those nodules only were tubercles, which developed after inoculation with tuberculous matter, while nodules appearing after inoculation with non-tuberculous substances, were not tubercles—an assertion which is as arbitrary as that of *Vines* and *Erdt*, that the nodules artificially produced by them were malleus nodules.

The assertions of *Villemin* were soon after advocated by *Lebert*.² He endeavored to strengthen the

¹ Experimentelle Beitræge zur Lehre von der Embolie. Virchow's Archiv. Bd. 25, 1862, p. 459.

² Allgem. Med. Central-Zeitung, 1866.

theory of *Villemin* by microscopical examinations of inoculation-tubercles. He found that many tubercles of man and inoculation-tubercles of animals possessed exactly similar structures.

Soon after, however, *Lebert*, in the course of new and more extended investigations, began to oppose the views of *Villemin*. This series of experiments was made in conjunction with *O. Wyss*.¹

Lebert and *Wyss* accepted the inoculation experiments of *Villemin* with tuberculous matter, but opposed his counter-experiments and the conclusions which he drew from them.

What strikes me, as the point of greatest interest in the article of *Lebert* and *Wyss*, is the observation, that nodules developed themselves in a dog, in which—for the sake of other experiments—they had made a fistula of the gall-bladder. The animal, though in perfect health on the day of the operation, died thirteen days afterward, and a post-mortem examination showed numerous nodules scattered throughout both lungs.

Lebert and *Wyss* made still other experiments. They injected, as did *Renault* and *Bonley*, pus, carcinomatous substances, mercury, and charcoal, into the jugular vein and trachea of different animals.

All these procedures were followed by a more or

¹ Beiträge zur Experimental pathologie, etc. Virchow's Archiv, Bd. 40.

less intense development of nodules in the lungs and the liver. They also introduced cheesy pneumonic products, and found thereafter nodules both at the place of inoculation, and in the lungs and the liver.

Lebert and *Wyss*, therefore, pronounced the nodules developing after injections into the blood-vessels to be tubercles, and agreed with *Panum* in regarding them as of embolic origin; and, since the nodules produced after these injections were similar in their anatomical characteristics to those which developed in the course of subcutaneous inoculations, they declared also these inoculation-nodules to be of the same origin.

They thought that, at the place of inoculation, peculiar fluids were formed, which found their way into the circulation, and thus led to a blocking up of the capillaries.

There is scarcely room for doubt, that the embolic theory, as applied to nodules developing after injections of wax emulsions, charcoal, and mercury, is correct; for emboli may certainly be formed, inasmuch as small particles of the injected material have been found in the nodules. The theory, however, that nodules produced by subcutaneous inoculations represent emboli, was not established by *Lebert*; and the anatomical similiarity of these nodules to those produced by venous injections, is not sufficient to warrant the acceptance of this view; for we have already seen, that histological investigations have proved, that tubercles may develop in endothelial

membranes in regions, indeed, which are entirely destitute of blood-vessels.

Although *Lebert* and *Wyss* did not prosecute their investigations in new channels, nevertheless, great credit belongs to them for having demonstrated conclusively, that the counter-experiments of *Villemin* were not to be regarded of such great importance as the advocates of the infection theory attached to them. Those experiments of *Lebert*, resulting in successful inoculation with cheesy and carcinomatous matter, claim special attention, since the experiments of *Villemin* with similar substances were followed by negative results.

Lebert and *Wyss* had, for these reasons, opposed the counter-experiments of *Villemin*, and conceded this much only—that inoculations with tuberculous matter were more often successful, than were those with indifferent substances. Soon after, *A. Vogel*¹ showed, that inoculations with tuberculous matter also often completely failed. His experiments, however, were not very extended: he inoculated only a cat, a crow, and a horse; nevertheless, they are mentioned here for reasons to be given later.

Notwithstanding the investigations and conclusions of *Lebert* and *Wyss*, the majority of experimenters adhered to the theories of *Villemin*. The virulency

¹ Die Uebertragbarkeit der Tuberculose. Deutsches Archiv für Klinische Medizin. Bd. II., 1864.

of tuberculosis was considered proved beyond all doubt, and the question, whether cheesy substances might produce tuberculosis in animals, was the only one left open for discussion. To this discussion belong the labors of *Hoffmann*,¹ *Hèrard* and *Cornil*,² *Genoudet*,³ *Roustan*,⁴ *Colin*,⁵ *Pidoux* and *Paul*,⁶ *Marcet*⁷, and *Petroff*.⁸

As to the results of the investigations of these writers, I will mention only that *Hèrard* and *Cornil* did not at first observe the development of nodules after the inoculation of cheesy pneumonic materials; and, on this account, they looked upon caseous pneumonia as an entirely different and distinct process from tuberculosis. Soon after, however, as these same observers continued their experiments with inoculations of pneumonic products, positive results followed, and they then declared caseous pneumonia and tuberculosis to be identical diseases.

In scanning the history of tuberculosis by inoculation, we find several instances of these rapid changes of opinion, inasmuch as the results of an experiment,

¹ Deutsches Archiv für Klin. Med. Bd. III., 1867.

² La phthisie pulmonaire. Paris, 1167.

³ Gazette Hebdom. de Paris. 1867.

⁴ Recherches sur l'Inoculabilité de la Phthisie. Thèse de Paris, 1867.

⁵ Acad. de Médecine, 16 Juli, 1867, und L'Union Méd., 1868.

⁶ Acad. de Médecine, 18 Feb., 1868. Paris.

⁷ Med. Chir. Transact. L.

⁸ Virchow's Archiv, 1868. Bd. 44.

admitting of two or more interpretations, were often interpreted according to preconceived opinions.

In regard to the investigations of *Colin* I may say that he was delegated by the Academy of Medicine, in Paris, to investigate the experiments of *Villemin*.

Colin corroborated *Villemin's* statement, that inoculation of tuberculous material leads to the development of nodules; but it should be noted that *Colin* pronounces everything cheesy, "tuberculous." In this sense he considered the entozoic nodules from the lungs of ruminants as tuberculous, and used them for inoculations. His inoculations were followed by positive results, and on this account he accepted the inoculability of tuberculous substances.

The development of nodules, after inoculation with entozoic nodules, deserves our especial consideration, also, in another direction. *Villemin*, as will be remembered, failed to observe the development of nodules after inoculations with these nodules, and, for this reason, regarded these investigations as counter-experiments in favor of his theory. The investigations of *Colin*, however, made it appear very probable that *Villemin* allowed himself to be deceived by an accidental failure. We are, therefore, justified in regarding the counter-inoculations of *Villemin* with entozoic nodules, as destitute of all the value and importance which he attached to them.

The experiments of *Pidoux* and *Paul* are valuable, because they show us that even the inoculations of tuberculous matter into animals which show a special predisposition to the development of nodules, often prove negative. They inoculated six rabbits with the sputa, and contents of cavities of phthysical persons, and in only one of these did they find any evidence of infection, and that but a single cheesy nodule of the size of a pea in the lung.

In another place I have called attention to the investigations of *Vogel*,* whose inoculations with tuberculous materials were negative. The objection, however, might be raised to *Vogel's* results, that the failure of the inoculations was due to the immunity of the animals inoculated. An entirely different state of affairs prevails, however, in the experiments of the investigators just mentioned. Rabbits are susceptible, in a high degree, to the development of nodules; but, notwithstanding this fact, the inoculations of most of the rabbits experimented upon, proved failures. We must, therefore, come to the conclusion, from the reports of *Pidoux* and *Paul*, that inoculations with both tuberculous and non-tuberculous materials, even under most favorable circumstances, are often not followed by infection.

Marcet added to *Villemin's* investigations by inoculating rabbits with blood and pus from tuberculous

*See page 60.

individuals, which gave positive results, and led him immediately to identify the nodules produced with tubercles. He even proposed to utilize these results as tests in making a differential diagnosis at the sick bed.

Opposed to this series of investigations, we find another series from which it was deduced: First, that inoculations with non-tuberculous matter also produce nodules; secondly, that nodules developed by inoculation are not, without further evidence, to be considered of the same character as human tubercles; and, finally, that nodules may even make their appearance as a result of traumatic influences.

I will give a brief sketch of these experiments and investigations.

*Empis*¹ who, as was mentioned before, regarded tuberculosis as a peculiar diseased process which he termed "granulie," acknowledged the great similarity between inoculation-nodules and his granulie of man, but strenuously opposed the idea of identifying the two processes, since the animals in which he produced nodules experimentally, although they remained under observation for more than a year, never manifested any general symptoms such as are observed in the progress of granulie.

*Feltz*² and *Clark*,³ led by the same motives as

¹ Bericht bei dem Internat. Congress in Paris, 1867.

² Gaz. Med. de Strassbourg, 1867.

³ The Medical Times, 1867.

Empis, declared against the identification of nodules produced by the inoculation of tuberculous matter with tubercles found in man.

Empis,¹ showed in a later publication that inoculations of pus, from puerperal peritonitis, typhoid ulcers, etc., and particles of inflamed croupous lung, *Behier*,² that injection of fat into the veins, *Clark*,³ that inoculations of the most varied non-tuberculous materials, were followed by the development of nodules.

Of much greater importance are the investigations of *Simon* and *Sanderson*,⁴ and *Wilson Fox*.⁵ *Simon* and *Sanderson* showed that inoculations of guinea pigs and rabbits, not only with tuberculous substances, but also with pyæmic pus, and that even long-continued suppuration produced by means of a seton, lead to the development of a marked miliary tuberculosis of the lungs, the pleuræ, the liver, and the peritoneum.

Wilson Fox,⁶ from experiments on one hundred and seventeen guinea-pigs and twelve rabbits, came to the same conclusion. *Fox* conducted his inoculation experiments with tuberculous and non-tuberculous materials, and also used setons through the skin. All

¹ Bericht des Internat. Congresses in Paris, 1864.

² L'Union Medicale, 1868.

³ L. c.

⁴ British Med. Journal, 1868.

⁵ British Med. Journal, 1868. The Lancet, 1868.

⁶ Lecture on the artificial production of tubercle, Royal Collegé of Physicians, 15 May, 1868.

were followed by either a localized or a disseminated production of nodules.

I have already called attention to an experiment of *Lebert* and *Wyss*, in which nodules developed in a dog, in consequence of traumatic influences. So long as this experiment stood isolated, it was not possible to use it as evidence; for nothing could be said in reply to an assertion that the animal did not become tuberculous on account of the trauma. But since *Sanderson* and *Fox* also observed the development of nodules after traumatic lesions, this experiment of *Lebert* and *Wyss* becomes significant.

Later *Lebert*¹ strengthened his theory that tubercles might be developed traumatically by the report of four clinical cases, in which phthisis developed in perfectly healthy individuals as a result of traumas of the lung. The consideration of the value of their evidence, I leave to the clinicians.

Wilson Fox also carefully examined, microscopically, artificially-produced tubercles, and his conclusion was that no perceptible difference existed between these and tubercles of man. In view of the results of their inoculations, and also in view of the microscopical similarity between the two, both *Sanderson* and *Fox* most emphatically denied the specific character of tuberculosis.

Almost simultaneously with *Fox*, *Bizzazero*² exam-

¹ *Revue Mensuell*, 1878, *Medil Centralblatt*, 1878, No. 13.

² *L'Union Med.* 1868.

ined the nodules produced by inoculation with tuberculous substances, and found them exactly similar in structure to true gray miliary tubercles.

I have shown, in preceding pages, that it is not always possible by the aid of the microscope to determine whether or not a pathological product is tuberculous in character. From this consideration it is easily understood how *Clark*,¹ on the one hand, saw in the nodules produced by inoculation with tuberculous matter and the tubercles of man, different formations, while *Sanderson*, *Fox*, and *Bizzuzero*, regarded the nodules from inoculation, not only with tuberculous, but also with indifferent substances, as exactly the same as true tubercles of man.

The important point of the matter, however, if I may be permitted to make the remark, is not in this difference of opinion concerning the histological character of these nodules, but in the fact that observers, confessedly trustworthy, had produced so-called tuberculosis by inoculation with these substances. Notwithstanding this fact, however, I will furnish further data, concerning these differences of opinion.

Langhans,² who microscopically examined nodules produced by inoculations with both tuberculous and non-tuberculous substances, acknowledges that there

¹L. c.

²Die Uebertragbarkeit der Tuberculose. Habilitationsschrift. Marburg, 1857.

is a certain similarity between these and human tubercles, but does not think that we are warranted in coming to any conclusion as to the identity of the two, simply from their anatomical similarity.

The following is a summary of the results of *Langhans's* observations :

1. The nodules are never present (He has reference here only to his own experiments)—in such numbers as are human tubercles.

2. They never produce any local destruction of the lung tissues.

3. The tubercles found by *Villemin* in the spleen, the kidneys, and the liver, are entirely different in structure from the nodules occurring in the lungs.

4. Similar nodules to those produced by inoculation, are often found in rabbits that have never been inoculated. They are then due to the presence of entozoa (*strongylus commutatus*).

5. The changes occurring at the place of inoculation, and the peculiar appearance of the skin, which *Villemin* pronounces tuberculosis, can be produced by various similar methods.

Langhans is inclined, in view of these facts, to believe that artificially-produced nodules are not at all identical with human tubercles, and, indeed, *that they are not even the product of the inoculations*, A thorough and scrutinizing examination of his evi-

dence, shows that he went a little too far in his conclusions.

His first and second conclusions were drawn solely from the experiments which he himself made on rabbits. The investigations of those observers, who claim that they have seen large numbers of nodules produced and also destruction of lung tissue following their production, are not taken into consideration by him

His third point is of little weight, for human tubercles, as the very recent investigations of *I. Arnold*¹ show, are characterized by differences in structure, according to the stage of their development and their location.

The fourth conclusion, too, loses value, when we consider that it has been deduced only from the results of his own experiments. Notwithstanding all this, however, *Langhans* deserves much credit for having called attention to the presence of entozoa as a source of error.

A short retrospect of the investigations so far undertaken, shows that inoculation of tuberculous as well as non-tuberculous matter, and also injections of various fluid substances into the blood-vessels, and, finally, traumatic influences, are capable of producing nodules in various animals.

¹ Virchow's Archiv. Bd. 82, 1880; Bd. 83, 1881; Bd. 88, 1882.

Furthermore, it follows from these various experiments, that the identity of artificially produced nodules, with human tubercles, has not been settled beyond all doubt and question. And, finally, we can conclude, even should we acknowledge, in conformity with the theory of *Villemin*—that the nodules following inoculations are in fact the exact counterparts of tubercles found in man—that, nevertheless, the specific character of tuberculosis can not be regarded as proved, if we consider the results of inoculations with indifferent materials.

This seemed to be about the condition of the question in 1868. It will be shown that subsequent investigations have changed matters but little. I will, nevertheless, speak of the later inoculations somewhat fully, since these experiments stand in intimate relation to the hypothesis recently advanced—that the virus of tuberculosis is a *contagium animatum*.

*Waldenburg*¹ made a great variety of experiments by inoculating seventy-one rabbits, twenty-eight guinea-pigs, one porcupine, one goat, and three horses.

These experiments gave the following results :

1. Inoculations with tuberculous matter, were, in many cases, not followed by infection. The results of the inoculations were not so certain as *Villemin* reported. The most successful results were produced by inoculating with softened tubercles; and the nodules thus developed presented the most complete

¹L. c.

analogy to human tubercles. In one case tuberculosis of the intestines was brought on.

2. Inoculations with caseous, non-tuberculous lymphatic glands, were followed by most surprising and startling success. In this set of experiments, too, a case of tuberculosis of the intestines developed. The material inoculated, if taken from living individuals, produced little reaction at the point of inoculation; the formation of nodules, nevertheless, became well marked, and extended throughout the body.

3. After inoculations with catarrhal pharyngeal sputa (which had been treated with alcohol and permanganate of potash), a disseminated development of nodules took place.

4. Inoculations with pus, taken from an abscess formed at the point of inoculation in the animals inoculated with pharyngeal sputa, were followed by like success.

On the whole, the experiments referred to under headings (3) and (4) did not succeed as often as did inoculations with tuberculous or scrofulous matter.

5. Inoculations of tuberculous and scrofulous matter which had been preserved in alcohol for months and then washed with boiling water, were followed by greater success than inoculations with similar fresh materials.

In some cases *Waldenburg* observed, in addition, an extended production of nodules; also ulcerations of the intestines, caries, etc.

6. Inoculations, even with tuberculous material,

that had either been treated with fuming nitric acid or had been thoroughly boiled in water, still led to an evident production of nodules.

7. *Waldenburg* observed the most startling results, however, after inoculations with non-tuberculous pharyngeal sputa that had been treated with alcohol or nitric acid. Nodules were developed extensively almost throughout the whole body (lungs, serous membranes, liver, kidneys, heart); large cavities were formed in the lungs and the spleen, and iritis and keratitis developed in some cases.

8. Inoculations with fluids from the organs of tuberculous and scrofulous individuals, which had been colored blue with aniline, produced disseminated nodules, which contained particles of aniline.

9. Subcutaneous injections of aniline likewise led to the development of nodules, but less frequently, and these, also, contained particles of the coloring matter.

10. Inoculation of a guinea-pig with boiled pig's blood produced nodules in the liver and the spleen.

11. Inoculations with pathological products, which had been made completely soluble by nitric acid, did not produce nodules.

These results led *Waldenburg* to come to the following conclusions :

The acceptance of a specific tubercle-virus is not justified ; for not only inoculations with tuberculous substances, which had been treated with nitric acid or

washed in boiling water, but also inoculations with non-tuberculous substances produce nodules having the same pathological significance. Since inoculations with the most various substances led to the development of nodules, we must ascribe to all these substances the capability of producing tuberculosis. This capability must be due to a physical property common to all of them. A comparison of these substances shows that, of all their physical properties only one can be taken into account in this connection, and that is the peculiarity that all these substances are composed of "*corpuscular elements*." *Waldenburg* thus thought—influenced, probably, to a great extent by the ideas predominating at that time in pathological histology—that these minute bodies gained entrance into the circulatory system by absorption, and there acted upon the white blood-corpuscles in such a way as to make them migrate, and thus give rise to the formation of miliary tubercles.

It soon became evident, however, that the theory of *Waldenburg* was lacking in one essential point, and was not so well-grounded as it had been originally supposed. The doctrine of *Waldenburg*, that inoculations with various indifferent materials gave rise to nodules, remained, as I shall soon show, unquestioned. Neither was it disputed that inoculation with substances which are corpuscular, leads to the development of nodules. What was doubted, and properly,

too, was that the "corpuseular elements" gave rise to a cell-migration, and in this way to the formation of nodules. www.libtool.com.cn

The fact that these minute bodies entered into the circulation, and here manifested themselves as foreign bodies, had already been partially proved by *Panum*, and was, therefore, only corroborated by the inoculation experiments of *Waldenburg* with colored substances. There were, however, no plausible grounds for supposing that these nodules were produced by the migration of white blood-corpuscles. Soon after the publication of the investigations of *Waldenburg*, it came to be generally conceded by histologists, as was mentioned above, that tubercles of the serous membranes might develop from endothelial cells, without involving the participation of blood-vessels.

This view was taken by *Dr. Fonlis* after numerous inoculation experiments.

*Dr. Fonlis*¹ introduced indifferent substances—pulverized cork and cinnabar—into the peritoneal cavity of guinea-pigs and developed tubercles in the peritoneum, and submitted them to a most careful microscopical examination. The result of these experiments was the conclusion, that these nodules possessed the same structure as tubercles of man and originated from the endothelial cells of the peritoneum. The changes which take place in the endo-

¹A Study of Tubercle. Glasgow Med. Journal. 1875.

thelium are described by him in the same manner as by *Kundrat* and *Th. Hering*.

From his observations, he disputes the theory of *Waldenburg* regarding the origin of tubercles, and makes the correction that miliary tubercles represent inflammatory centers produced by the irritation of very minute bodies.

With this correction, the theory of *Waldenburg* was fully in conformity with the results of histological, as well as experimental, investigations.

Soon after the appearance of *Waldenburg's* articles, a publication of *Klebs*¹ appeared, in which he instituted a re-examination of the statements of *Lebert* and *Wyss*, and *Waldenburg*.

Klebs, in the first place, confirmed the correctness of *Villemin's* statements. Of the investigations of *Klebs*, I shall mention only that he used tuberculous material from a negro subject for his inoculations; and, furthermore, that he succeeded in developing nodules in dogs. *Klebs* also extended and added to the theories of *Villemin*, in that he declared that the so-called tuberculous virus was not soluble in water, alcohol, or ether; for inoculations with extracts which had been made from tuberculous substances with the aid of these liquids proved inoperative. He also instituted counter-experiments on two dogs with carcinomatous material, the result in both cases

¹ Virchow's Archiv, Bd. 44. 1868.

being negative. From these observations, *Klebs* joined the ranks of those who saw in tuberculosis a specific disease. He supported his view also by the following consideration: The nodules which develop after the inoculation of indifferent substances can not be true tubercles, since they do not possess the character of "progression;" only those nodules are identical with tubercles which are developed after inoculation with tuberculous substances. *Klebs*, however, was not justified in this conclusion, for the following reasons: 1st. The investigations of *Waldenburg*, *Saunderson*, and *Fox*, have shown clearly that nodules developed by inoculation with indifferent substances are just as progressive as those following inoculations with tuberculous materials. The animals become more and more emaciated and finally die, and post-mortem examinations show that not only one, but many organs of the body, contain numerous nodules. 2d. The nodules developed by inoculation with tuberculous materials are not always, as *Empis* has demonstrated, progressive in character; often they are limited to one organ, and the animals appear perfectly healthy. This point, however, was well-known to *Klebs*; but he has interpreted it in a different and entirely unwarranted way in forming his conclusions; he says that, in those animals in which post-mortem examinations showed tubercles produced by inoculation only in a certain organ, the nodules had been present, nevertheless, in several organs, but

had undergone a healing process. No one will doubt that tubercles may heal; but that they heal without leaving the least trace of their former presence is a point which *Klebs* should have endeavored to prove. Without this proof it might be said, with equal force, that all individuals and animals are tuberculous, and that the tubercles had generally healed in such a manner that they are not visible in a post-mortem examination.

The assertion of *Klebs*, therefore, that the nodules appearing after inoculation with indifferent substances, have a different pathological significance from those occurring after inoculation with tuberculous matter, is to be regarded as not proved.

His other statement, too, that the virus of tuberculosis is not soluble in water, alcohol, or ether, rests upon a very weak foundation. There is an old proverb which says, "Never hang a murderer until you catch him!" It was necessary to have the virus before being able to prove its insolubility. *Klebs* has merely taken the existence of a virus for granted. That tuberculous matter contained a virus was only a theory of his own, of the truth of which, as I have shown, he has given no proof. It is, therefore, immaterial to our present discussion whether or not the inoculation of aqueous, alcoholic, or ether extracts, develops tubercles, and especially so since *Klebs* himself published that in two dogs upon which he experimented, inoculation with tuberculous matter

was perfectly unsuccessful. If this was true, why should not extracts from tuberculous matter which are, perhaps, mechanically less irritable, under certain circumstances, remain unsuccessful?

The investigations of *Waldenburg* make it evident that the facts are not always as *Klebs* affirmed.

But, finally, we have the testimony of an authority upon this subject, of one whose evidence is of even more importance than that of *Waldenburg*, and that is *Klebs* himself. *Klebs*, in a subsequent publication,¹ abandoned his claim that the virus of tuberculosis was insoluble in water and alcohol, and declared that it was perfectly soluble in these fluids.

Some years after, *Cheveau*² again denied the solubility of the tubercle-virus, and all his inoculations with filtrated tuberculous matter proved unsuccessful. It seems to me that both this statement and the concession made by *Klebs*, illustrate very forcibly the unreliability of the evidence derived from inoculation experiments.

The investigations of *Cohnheim* and *Fraenkel*,³ the results of which were directly opposed to the theory of the specific character of tuberculosis, were published almost simultaneously with those of *Klebs*. I give a sketch of their experiments.

¹ Virchow's Archiv, Bd. 49, 1870.

² Recueil de Méd. véter, 1872.

³ Experiment. Untersuchungen über die Uebertragbarkeit der Tuberculose. Virchow's Archiv, Bd. 45, 1869.

The following substances were introduced into the peritoneal cavity of guinea-pigs: 1. Tuberculous and cheesy materials. 2. Particles taken from tuberculous human subjects, the particles being devoid of tubercles, however. 3. Particles from condyloma, sarcoma, carcinoma, and inspissated pus. 4. Perfectly normal substances. 5. Small pieces of tissue paper, lint, gutta-percha, caoutchouc, and cinnabar. 6. Finally, pus from various sources was injected into the vena jugularis of three dogs. In all these experiments an extended development of nodules took place, provided the animals outlived the operation for some time.

Cohnheim and *Fraenkel* therefore adopted the following view of the nature of these nodules: "All the characteristics by which tubercles distinguish themselves as such, presented themselves here. Both in their extended dissemination through the different organs and also in their macroscopical and microscopical structure, the similarity to miliary tuberculosis could not have been more perfect. The untenableness of the doctrine of 'specificity' was, therefore, fully démonstrated by these experiments. This result, as unexpected as it at first was to us, could not but impress us by its constancy."

Cohnheim and *Fraenkel* furthermore claimed that "it was in reality the entrance of the inspissated pus into the circulation that gave rise to tuberculosis," and, for this reason, they regarded tuberculosis produced by

inoculation, as a "traumatic tuberculosis." This last disease is to be distinguished, according to these experimenters, as different from the "idiopathic tuberculosis of man." We see from the foregoing that *Cohnheim* and *Fraenkel* have really only repeated the experiments of *Saunderson* and *Fox*.

Notwithstanding this last fact, however, their efforts deserve prominence for two things: First, the sharp division they made between idiopathic and traumatic tuberculosis, and secondly, the great constancy of the results of their inoculations.

On the first point I make the following notes: I have more than once called attention to the manifold interpretations which have been placed upon the nodules produced by inoculation. Sometimes they have been regarded as counterparts of true tubercles, without reference to the inoculated matter used; sometimes as counterparts of malleus nodules; again, those only were considered true tubercles which developed after the inoculation of tuberculous matter; and at other times all nodules, without reference to the materials inoculated, were traced back to pathological processes that had nothing in common with tuberculosis.

Cohnheim and *Fraenkel* regarded all nodules developed by them, no matter what the material inoculated was, as tubercles; but they made a sharp distinction between tubercles produced by inoculation and idiopathic tubercles of man. But what are idio-

pathic tubercles? It appears, from his publication, that *Cohnheim* regarded idiopathic tubercles as those having a peculiar and unknown cause. It can not be doubted that *Cohnheim* and *Fraenkel* made their experiments with a view of learning this unknown cause. The experiments seemed to indicate, that inspissated pus which gains entrance into the circulation develops the tubercles. But this indication may be true or false, according as the experiment and the observation were accurate or inaccurate. *Cohnheim* and *Fraenkel* were, however, firmly convinced that their experiments were faultless, since "the similarity between the tubercles produced (by them) and the tubercles of man could not have been more perfect." Consequently one would expect to find them announcing the conclusion which their experiments indicated, viz: Tuberculosis can be developed; we have developed it; therefore the cause, or at least one of the causes, has been found. But we find them doing nothing of the kind. They regard the indication which their experiments gave them as both correct and incorrect, and declare the tuberculosis experimentally produced by them to be as entirely different from tuberculosis of man, and affirm that the cause of tuberculosis of man is still as much shrouded in mystery as before.

I come now to speak of the second point in question—the constancy of the results in their inoculations. It was mentioned that numerous experiment-

ers attributed the frequent failure of their inoculation experiments to the want of predisposition on the part of the animals operated upon. *Cohnheim* and *Fraenkel* never had the opportunity of maintaining such a theory, for all their inoculations were followed by striking success. They failed in some of their experiments, it is true, but the reason for this, they explained, was the death of some of the animals from peritonitis soon after the inoculation. In all the remaining cases, they found, contrary to the experience of many other investigators, not only the development of nodules, but also a dissemination of these nodules through almost all the organs of the body, such as occurs only in the worst forms of miliary tuberculosis.

Something strange, however, took place soon after. *Cohnheim*¹ and *Fraenkel*, after the publication of the results of these experiments made in Berlin, repeated the inoculations with indifferent materials in Breslau, but *without success*. No tubercles made their appearance; and, in conformity with these later results, *Cohnheim* now declared himself in favor of the specific character of tuberculosis. He still, however, regarded the nodules developed by his inoculation experiments in Berlin as tubercles, but denies that the nodules were the product of inoculation, supposing

¹ Allgemeine Pathologie. Die Tuberculose vom Standpunkte, etc.

that the animals had been infected in the rooms of the institution at Berlin.

A careful writer would, perhaps, have said, "might have been infected;" for the animals experimented upon were probably all dead by this time, and, therefore, *Cohnheim* had no evidence whatever in Breslau and Leipsic to prove the infection supposed to have taken place in the institution at Berlin. Nor was any evidence advanced to demonstrate the possibility or probability of an infection of animals that were shut up together in the same quarters. *Cohnheim* himself has never published, either from Breslau or Leipsic, any investigations that would indicate such an infection as probable, and he has ignored every scientific precaution by his positive assertion that "the animals in the institution at Berlin had been infected."

One more circumstance in the investigations of *Cohnheim* also requires mention. In most of the counter-experiments undertaken in Breslau and Leipsic, by which he tried to prove the impossibility of the success of inoculations with indifferent substances, the material inoculated was not introduced into the peritoneal cavity, as in Berlin, but into the aqueous chamber of the eye.¹ I shall not dispute that by this last procedure the technic of inoculation has been advanced. Nobody, however, will claim that these inoculations in the aqueous chamber can be regarded as

¹ *Cohnheim und Salmonsens, Sitzungsberichte der Schlesischen Gesellschaft, 1878.*

counter-experiments to those inoculations which were made in the peritoneal cavity.

If *Cohnheim* desired to prove by counter-experiments that the investigations instituted at Berlin were untrustworthy and not reliable, he should have made a sufficient number of experiments in Breslau and Leipsic, making his inoculations in the same way. The records on this subject, especially the investigations of *Baumgarten*,¹ teach us that inoculations into the aqueous chamber are not, as a rule, favorable to success. I much incline to the acceptance of the statements of *Baumgarten*, so far as inoculations with indifferent substances are concerned.

About this time *Hänsell*² had observed that inoculations in the aqueous chamber of the eyes of rabbits, with pus from syphilitic gummata, may lead to the formation of nodules in the iris, the lungs and the liver; and I am convinced myself of the correctness of these observations.³

The aqueous chamber experiments of *Cohnheim*

¹ Berliner Klin. Wochenschrift, 1880, No. 49.

² Archiv. für Ophthalmologie, 1881. Vorläufige Mittheilung über Versuche von Impfsyphilis.

³ Hänsell regards the nodules as products of the inoculated syphilis. [This would make the first case on record where gummata have been transmitted by inoculation; this has never happened on man. Professor Stricker, in a discussion on that subject, remarked that these products must be regarded rather as tubercles. Wiener Med. Wochenschrift, Feb. 24, 1883, No. 8. E. E. S.]

may, in view of this experiment of *Hänsell's*, be subjected to another criticism. *Cohnheim* claims that the introduction of tuberculous and scrofulous substances only, will develop tuberculosis, and, for this reason, inoculations in the aqueous chamber were well suited for demonstrating, in a striking manner, the connection of scrofulosis with tuberculosis. But it follows from *Hänsell's* experiments that pus from gummata, introduced into the aqueous chamber, leads to the same successful result; it consequently follows, according to *Cohnheim's* argument, that by inoculations in the aqueous chamber, the identity between tuberculosis, scrofulosis, and syphilis, has been demonstrated.

The aqueous-chamber experiments of *Cohnheim* were subsequently repeated with variable success by *Salomonsen*,¹ *Hänsell*,² *P. Baumgarten*,³ and *Schuchardt*.⁴

While *Salomonsen*, *Hänsell*, and *Schuchardt* were able, in almost all cases, to develop with the most varied tuberculous and cheesy materials both a production of nodules localized at the point inoculated, and also a disseminated development of nodules involving almost all the organs of the body, similiar inoculations by *Baumgarten* were at first followed by "absolute failure," and only some of his later experi-

¹ Nordisk. Med. Arkiv, 1879.

² Archiv. für Ophthalmologie. Bd. XXV.

³ Berliner Klin. Wochenschrift, 1880, No. 49.

⁴ Virchow's Archiv, Bd. 88, 1882.

ments were followed by positive results. *Baumgarten* therefore disputes the constancy of the inoculability of tuberculous materials. Inoculations with pearl-nodules (murrain) only, gave constant results.

Hänsell, as well as *Baumgarten* and *Salomonsen*, also made counter-inoculations with different substances, but were never able to find nodules following. *Hänsell* and *Baumgarten*, in view of these results, placed themselves on the side of *Cohnheim*; but, as I have before shown, *Cohnheim* himself was on the wrong side. The wrong side certainly does not become the right one simply because *Hänsell* and *Baumgarten* place themselves on that side. I have already mentioned that *Hänsell* developed nodules by introducing into the aqueous chamber, pus from gummata. *Baumgarten*, on the other hand, makes this remark: "For this purpose I developed the most different degrees of panophthalmitis with the most varied organic and inorganic substances, traumas, chemical substances, and septic materials." From this it follows that *Baumgarten*, in his counter-inoculations, produced panophthalmitis. A condition of the utmost importance in every inoculation certainly is that the inoculated material should become absorbed. If, however, the inoculated bulbus suppurates, and panophthalmitis is developed, it becomes very questionable whether or not the inoculated material is absorbed readily. We can not therefore

regard the counter-experiments of *Baumgarten* as absolutely satisfactory.

The more recent investigations of *Baumgarten*¹ and *Damsch*² do not change the situation in any way. *Baumgarten* inoculated blood from tuberculous individuals into the aqueous chamber of the eye, and succeeded in developing nodules in the iris. In the counter-experiments, in which septic blood was used, the inoculated bulbus was, as in former cases, destroyed by suppuration, and the importance of these investigations as counter-experiments can not therefore be granted, for the reasons mentioned above.

Damsch, on the other hand, used urinary sediments from individuals with tubercular affections of the genito-urinary system, and caused the formation of nodules in the iris. He made no counter-experiments, but, nevertheless, recommended the use of these inoculations for diagnostic purposes.

I might omit all criticism here of these inoculation experiments, since the most important point they establish, even in the most favorable cases, is that the aqueous chamber is a very unsuitable place for the success of inoculations. All these negative results therefore can not be taken into consideration in opposition to the immense number of positive results gained by inoculation in the peritoneal cavity.

¹ Med. Centralblatt, 1881, No. 15.

² Deutsches Archiv für Klin. Medizin, 1882.

There was, however, no lack of observers who also failed in obtaining results by inoculations of indifferent substances into the cavity of the peritoneum. Besides those already mentioned, we find the following in the last decennium: *Bagge*,¹ *Chauveau*,² *Paraeskeva* and *Zallonis*,³ *Klebs*,⁴ *Bollinger*,⁵ *Orth*,⁶ *Petroff*,⁷ *Reinstadler*,⁸ *Hüter*,⁹ *Weichselbaum*,¹⁰ *Martin*,¹¹ and in part also *Pütz*,¹² and *E. Frerichs*.¹³

But if a very large number of trustworthy observers in every quarter of the globe and in numerous instances—say hundreds of times—have seen geese flying, the statement of a number of other men, that they had not been able to see geese flying, would not have much weight against the claims of the former.

However many experimenters there may have been who were unsuccessful in their inoculations, the num-

¹ Repertorium für Thierheilkunde, 1870-71.

² L. c.

³ Med. Centralblatt, 1872.

⁴ Archiv für Exper. Pathologie. Bd. I.

⁵ Archiv für Exper. Pathologie. Bd. I.

⁶ Berliner Klin. Wochenschrift, 1875.

⁷ Virchow's Archiv, Bd. 74, 1878.

⁸ Archiv für Exper. Pathologie, 1879.

⁹ Deutsche Zeitschrift für Chirurgie, VI.

¹⁰ Med. Centralblatt, 1882, No. 19.

¹¹ Med. Centralblatt, 1882, No. 44.

¹² Wiener Med. Blätter (Naturforscherversam, in Eisenach), No. 41, 1882.

¹³ Beitrage zur Lehre von der Tuberculose, 1882.

ber of positive results reported by others is too large (as far as recorded the positive are far more numerous than the negative) to be disregarded. That not every inoculation succeeds, is a fact I believe in all forms of inoculation. It is also conceded on all sides that not every animal experimented upon, is predisposed to the development of nodules; for inoculations with genuine tuberculous substances even, often fail. Another fact, too, which has been fully established, is that not all inoculated materials are alike potent and active as irritants. Certain indifferent substances seem to act with less irritation than tuberculous materials. In the latter, certain chemical elements are present, which are entirely wanting in the indifferent agents. What does it matter then, if a number of investigators have been unsuccessful in inoculating with indifferent agents? Is the whole doctrine of the specific character and contagiousness of tuberculosis to be founded on this?

*Bernhardt*¹ also expressed himself to the same effect. He made experiments on one hundred rabbits and six guinea-pigs, the inoculations being made, partly with tuberculous matter, partly with indifferent materials, and partly with tuberculous and cheesy substances which had either been boiled in water for hours or had been preserved for a long time in alcohol.

The results were: 1. That inoculations of cheesy

¹Deutsches Archiv für Klin. Medizin, 1869, and Mediz. Centralblatt, 1870. No. 18.

materials from phthisical individuals, led, in most cases, to the development of nodules, which were considered by *Bernhardt* as tuberculous from his own microscopical examinations. 2. That inoculations of rabbits even with the most infectious materials often fail. 3. That inoculations with indifferent substances also produce nodules, the period of incubation, however, being longer and the development of nodules not so extended.

Bernhardt's observation that guinea-pigs, the spinal cords of which had been punctured with a needle, developed nodules in different organs of the body, is of particular interest.

*C. A. Ruge*¹ also succeeded, after the introduction of particles of cork and sponge into the peritoneal cavity of guinea-pigs, in developing nodules. His investigations were conducted on twenty-seven guinea-pigs and two dogs.

*Gerlach*² announced furthermore that traumatic influences were sufficient to produce nodules (true tubercles he thinks) in rabbits and guinea-pigs, while in other animals, dogs, cows, sheep, goats, etc., inoculations even with tuberculous material were seldom successful.

*Th. Hering*³ also obtained similar results and claims

¹ Einige Beiträge zur Lehre von der Tuberculose. Inaug.-Diss., 1869.

² Virchow's Archiv. Bd. 51. 1870.

³ Histolog. und Experim. Studien über Tuberculose. Berlin, 1873.

in his article that inoculations with tuberculous materials are often unsuccessful.

At the same time *Papillon*, *Nicol*, and *Laveran*¹ asserted that inoculations of non-tuberculous substances produced cheesy centers with a general development of tubercles.

*Perls*² came to the same conclusion after the introduction of tissue-paper under the skin, and *Martin*³ after the injection of semen lycopodii into the veins. Inoculations with indifferent substances were undertaken by *O. Robinson*⁴ also. He obtained about the same percentage of successes and failures with his numerous inoculations with tuberculous material, as with those of non-tuberculous substances.

Special mention may here be made of an inoculation made by *Paraskeva* and *Zallonis* on a human subject. A fisherman, fifty-five years of age, suffering with gangrene of the big toe, was inoculated with the contents of a lung cavity. He died five weeks after the inoculation in consequence of the gangrene, and the post-mortem examination showed seventeen tubercles in the right lung, two in the left, and two on the surface of the liver. In consequence of this the experimenters decided that tuberculous substances are inoculable on the human organism. They advance,

¹ Gazette des Hopitaux, 1871.

² Allgemeine Pathologie, 1877.

³ Tuberculose des Sereuses. Med. Centralblatt, 1880. No. 42.

⁴ Med. Centralblatt, 1882. No. 24.

however, no proof of a causal relationship existing between the inoculation and the development of the tubercles. This experiment, therefore, does not disprove the observations that various indifferent substances also bring about a formation of tubercles. But an objection might be raised, to the effect that, in all those cases in which inoculations with these substances developed tubercles, the observers might have been deceived. The animals inoculated with true tuberculous matter were, perhaps, kept in the same quarters with those that had been inoculated with various indifferent substances. All were, possibly, cases of infection only.

The fact, however, that *Waldenburg* found small particles of the coloring matter inoculated, contained in the tubercles, is strongly opposed to this inference. The same fact is also noted by other more recent observers, whom I mention in this connection because they furnish data which will be used later.

*Grohé*¹ injected, sometimes into the veins and sometimes into the serous cavities of the animals experimented upon, gonoïdes of *aspergillus glaucus* and *penicillium glaucum*, and observed, on post-mortem examination, a disseminated production of nodules in the peritoneum, the diaphragm, the muscles, and the kidneys, as in miliary tuberculosis. The nodules contained in their centers, strings of fungi.

¹ Berliner Klin. Wochenschrift, 1870. No. 1, und Block's Inaug. Diss., 1870.

The experiments of *Grohé* were afterward repeated by *Grawitz*¹ with negative results. *Grawitz* explains the failure of his experiments with the supposition, that *Grohé*, without being aware of it, used an entirely different kind of fungi from the one he mentioned; for, when *Grawitz* inoculated with other forms than those mentioned by *Grohé*, he too obtained positive results. *Grawitz* inoculated rabbits with gonoïdes of *oidium lactis* and *oidium albicans*. *Grawitz* had learned from former experiments that the vegetation of the spores was possible, only when absorption of the inoculated material went on slowly; he, therefore, produced in the inoculated animals, according to the method of *Wegner*,² ascites, by the introduction of air into the peritoneal cavity. Post-mortem examinations showed that the peritoneum was dotted with nodules from those of the miliary form to those the size of a pin-head. The nodules in these experiments also contained threads of fungi.

Similar experiments were made by *M. Wolff*.³ Guinea-pigs were subcutaneously injected with Pasteur's fluid,⁴ which had been mixed with a drop of putrid blood, containing cocci and bacteria. The re-

¹ Beitræge zur system. Botanik, Virchow's Archiv, Bd. 70, 1877.

² G. Wegner, Chirurgische Bemerkungen, etc. Langenbeck's Archiv, 1876.

³ Ueber entzündliche Veränderungen. Virch. Archiv, Bd. 67, 1876.

⁴ [Pasteur's fluid is composed of crystallized sugar, tartrate of ammonia, well-burnt yeast-ash, and distilled water. E. E. S.]

sult of the inoculation was a development of nodules (sometimes of cavities) in the lungs and the liver.

Grohé and *Grawitz* both agreed that strings of fungi were found present in the nodules of the peritoneum. This is in perfect harmony with the observations of experimenters mentioned in preceding pages, that, after inoculation with colored substances, particles of the coloring matter were found in the nodules. If aniline blue or cinnabar is inoculated, the nodules contain minute particles of aniline or cinnabar; if portions of fungi are inoculated threads of fungi are found in the nodules.

Since it is in the highest degree improbable that nodules developed first and that granules of coloring matter, etc., were deposited in them afterward, hardly any other supposition is tenable except the one that the granules and threads of fungi reached their location first, and the nodules then developed around them. Possibly these minute particles may be regarded as microscopical foreign bodies, which induce, in certain animals, the formation of miliary inflammatory centers, and thus produce nodules. This supposition derives from the above-mentioned experiments of *Baumgarten* considerable support and strength. *Baumgarten*, as was seen, implanted directly into the animal tissues foreign bodies of microscopical dimensions, and thereby produced nodules which were identical in character with those produced by inoculation.

In view of the fact then, that not one case is reported in which healthy animals acquired tubercles by being confined with sickly ones; in view, also, of the fact that tubercles are, as a rule, found in close proximity to the places of inoculation; and in view, finally, of the fact that particles of the inoculated substances have been found in the tubercles produced, the objection raised on page 88 becomes void. We are justified, therefore, in concluding from the results of all inoculation experiments so far as known, that the specific character and contagiousness of tuberculosis are not proved.¹

¹The works of *Talma*, *Lustig*, and *Geigel*, were not at hand.

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CHAPTER III.

INHALATION EXPERIMENTS.

Inhalation experiments were introduced into the experimental pathology of tuberculosis by *Knauff*.¹

Knauff, in 1867, was the first to show that the continued inhalation of coal-dust produced in the pleuræ of dogs gray nodules, similar in structure to human tubercles.

In 1876, investigations similar to those of *Knauff* were taken up by *Ins*,² and in 1878 by *Ruppert*.³ *Ins*, as well as *Ruppert*, observed the development of nodules in the lungs of animals experimented upon; the former, after inhalations of pebble-dust, the latter, of lamp-black. Both of these experimenters reported that the nodules produced by the inhalations possessed great similarity to miliary tubercles.

Guenther and *Harms*⁴ tried the experiment of causing rabbits to inhale the air expired by tuberculous cows. The results were negative. Later *Tappeiner*⁵ and

¹ 41Versammlung deutscher Naturforscher zu Frankfurt.

² Untersuchungen über Kieselstaubinhalation. Arch. f. Exp. Pathol. Bd. V., 1876.

³ Ueber Kohlenstaubinhalation. Virchow's Archiv, Bd. 72, 1878.

⁴ Magazin für die gesammte Thierheilkunde, 1871.

⁵ Wiener Med. Presse, 1377.

*Lippel*¹, as well as *Schweininger*, added to the air inhaled particles of tuberculous sputa; in all these experiments the animals experimented upon (dogs) developed nodules, in some cases in the lungs only, in others in several organs at the same time.

The experiments of *Tappeiner* were repeated and extended by *M. Schottelius*. *Schottelius* used tuberculous as well as non-tuberculous substances (coal-dust, cinabar, Berlin blue, fæces, particles of fungi, débris of pigs' and sheep's brains, and Limburger cheese), for his inhalations. All the dogs experimented upon exhibited, after the lapse of several weeks, nodules in the lungs, no matter what substance they had inhaled. A difference in the intensity of the pathological changes was observed, however, in those cases where organic substances had been inhaled. Animals inhaling these substances showed, in addition to extensive inflammatory centers in the lungs, "caseation and cavities—processes having great similarity to certain forms of phthisis occurring in man." It may also be worthy of mention that the nodules produced contained particles of the inhaled substances.

In the same year, *Tappeiner*,² induced by the investigations of *Schottelius*, repeated his inhalation ex-

¹ Bericht der Naturforscherversammlung, 1877.

² Über eine neue Methode Tuberculose zů erzeugen. Virchow's Archiv. Bd. 74, 1868.

periments with tuberculous materials, and also made two counter-experiments. Two dogs were made to inhale the débris of sheep's brains; and, since these two experiments proved negative, *Tappeiner* opposed the views of *Schottelius*. The counter-experiments of *Tappeiner* were, however, too limited in number and in the variety of substances used for inhalation. *Schottelius* had inoculated eighteen animals with indifferant materials. Of what value and importance, then, are the two counter-experiments of *Tappeiner*?

Objections were again raised afterward to the experiments of *Schottelius* by *Weigert*.¹ *Weigert* denies that *Schottelius*, in his investigations, developed true tuberculosis, since the nodules in the animals experimented upon always made their appearance in the lungs only. This statement is certainly perfectly true; *Schottelius*, in his reports, speaks of nodules in the lungs only. But *Weigert* does not mention that the development of nodules was limited to the lungs in those animals also, which, in *Schottelius's* experiments, had inhaled true tuberculous matter.

The investigations of *Schottelius* teach, therefore, that the manner of distribution of the nodules is not a sufficient criterion of their nature. If one kind of nodule is tuberculous, the other must be also, and especially so—as *Schottelius* has shown—because both

¹ Zur Lehre von der Tuberculose, etc. Virchow's Archiv, Bd. 77, 1879.

forms of nodules are exactly identical in their microscopical as well as macroscopical characters.

The question, however, as to whether or not the nodules appearing after the inhalation of tuberculous matter, actually correspond to the tubercles of man, neither *Tappeiner* nor *Weigert* has answered.

This question should have been fully and satisfactorily settled, especially in interpreting the importance of nodules produced by inhalation; for the dogs which inhaled tuberculous substances were, in contradistinction to the animals that were inoculated with tuberculous matter, in good physical condition. They were frisky; the appetite and weight in most cases were not diminished; but few of them died from the effects of the inhalation, most of them being forcibly put to death for the examinations.

In a subsequent article *Tappeiner*¹ reported some inhalation experiments with pus from scrofulous lymphatic glands, made in order to determine the question as to the identity of scrofulosis and tuberculosis. All the experiments were followed by negative results; and, for this reason, *Tappeiner* opposed the doctrine that tuberculosis and scrofulosis were identical diseased processes

I have mentioned, in speaking of inoculation experiments, that inoculations with scrofulous substances, as well as with tuberculous matter, lead to an extensive development of nodules, and that inoculations in the aqueous chamber, even—as a rule

¹ Neue Experiment. Beiträge. Virchow's Archiv. Bd. 82, 1880.

unsuccessful—if made with scrofulous matter, often produce nodules. As opposed to all these successful experiments which, by the way, *Tappeiner* completely ignored his investigations, provided they were made very carefully, prove only that inhaled matter does not lead to the formation of nodules with the same certainty as inoculated matter.

Tappeiner made another experiment, also, by letting a tuberculous woman cough into a box in which several rabbits had been placed. Two months afterwards the animals were still in perfect health, which led *Tappeiner* to the conclusion that the air exhaled by tuberculous individuals does not infect, “for, if this were the case, both of the rabbits would surely have become tuberculous.”¹

¹[Dr. Janeway published in the Medical Gazette of Dec. 30, 1882, an example of the communication of phthisis from man to dogs. A young man had suffered from pulmonary tuberculosis for some months. He had a pet dog, a black and tan terrier, that was accustomed to sleep in his master's arms every night. The dog soon became affected with a cough, as was his master, having inhaled, as Janeway thought, the breath from the phthisical patient. All signs of tuberculosis rapidly followed, and the dog soon died. A King Charles spaniel was next procured, which rapidly followed the black and tan to the grave. A Scotch terrier, which was next bought, likewise became consumptive. This dog, however, survived his master, although he was affected with a severe cough, and was losing flesh and strength daily. E. E. S.]

*Giboux*¹ repeated these experiments with several slight modifications, and observed the formation of nodules in the lungs, the liver, and the spleen. If, however, the air inhaled was made to pass through carbolized cotton, the animals remained healthy, and, as a proof of the healthiness of the animals, it is mentioned, among other things, that they were eaten with impunity and with no bad ulterior results by the experimenter and his family!

Giboux promises to report counter-experiments in a later publication. The experiments with inhalations of phthisical sputa, were again repeated by *Bertheau*.² The results were the same as those arrived at by *Tappeiner*, with the exception that the production of nodules was always limited to the lungs.

Bertheau performed also, in one case, the experiment of causing inhalations from caseous lymphatic glands; the result was, contrary to *Tappeiner's* experience, the same as in inhalations with tuberculous matter.

Finally the investigations of *Weichselbaum* and *Balogh* must be mentioned.

*Weichselbaum*³ experimented on dogs, with inhalations of indifferent substances. These investigations showed that not only tuberculous sputa, but other organic substances (spleen of oxen and strong cheese) also produced similar tubercle resembling nodules,

¹ Med. Centralblatt, 1882. No. 40.

² Deutsches Archiv. für Klin. Medizin, Bd. xxvi.

³ Med. Centralblatt, 1882. No. 19.

but that tuberculous substances act with much greater intensity than non-tuberculous ones. *Weichselbaum* mentions the most astonishing fact, that in consequence of one inhalation of tuberculous sputa nodules were developed after the lapse of but one or two days

Finally *Balogh*¹ made inhalation experiments with rod-shaped bacteria which he had cultivated from putrid water from marshes. The results were positive. He reported his investigations and results before a society in Pesth, but a more general publication has not yet been made.

In looking over these various results of inhalation experiments, we see that they do not differ in any essential points from the inoculation experiments. Both have produced positive as well as negative results.

A complication of circumstances might however be present in inhalation experiments inasmuch as the inhalation of air, which possibly may contain certain volatile substances (I refer to chemical compounds that might be formed in the lungs of tuberculous persons), might in itself be a source of infection. It is also conceivable that the air proceeding from the lungs of persons afflicted with tuberculosis actually contains micro-organisms which are the real sources of infection. Finally it is possible,

¹ Vortrag gehalten in der Gesellschaft der Aerzte in Pest. Wiener Mediz. Blaetter, No. 49.

that the air inhaled contains finely divided bodies which, coming into the lungs of the animals experimented upon, act as irritants and in this way cause disease. In this last case the animals experimented upon would be subjected to the same influences as in inoculation, for a mechanical irritation would then be the most important factor in both.

Waldenburg's supposition that corpuscular elements, or, as I would better say, bodies in a state of minute division, must, in the first place, enter the tissues in order to produce nodules, would in this case receive additional strength.

Up to this time, however, experimenters, as the records show, have not studied inhalation experiments with this idea in view. They have, without sufficient examination, drawn a parallel between the air exhaled by the sick and air filled with particles of dried sputa and other organic matters. They commit the same error as did *Klebs* when he inoculated with aqueous or alcoholic extracts. The question should first have been settled, whether or not a poison was actually present; and, this having been established, experiments might then have been made as to its solubility.

Without doubt, inhalation experiments have taught us one thing: The inhalation of bodies in a state of minute division may produce nodules in the lungs. Granted that these nodules are not true tubercles; granted that, for the production of true

tuberculosis of man, something more—a peculiar disposition or constitution, perhaps—is necessary; the experiments, nevertheless, are of great value, in consideration of the fact that so large a percentage of the whole number of cases of tuberculosis occurs among those persons who work in an atmosphere saturated with dry organic particles.¹

¹ [*Schottelius* has recently called attention to a new anatomical peculiarity of the minute bronchioles. The reason why carnivora are less frequently affected with lung diseases than herbivora, is accounted for by *Schottelius* in the fact that the small bronchioles of the carnivora become narrowed together in the shape of funnels toward the alveoli, and on this account the causative elements of disease find great difficulty in gaining entrance; the herbivora, on the contrary, have wide bronchioles. The bronchioles of man sometimes approach the type of the carnivora, sometimes that of the herbivora. The last condition *Schottelius* considers as a kind of hereditary predisposition which would make the acceptance of a peculiar contagium superfluous. Possibly this condition might also exert some influence in the production of nodules in inhalation experiments.

Virchow's Archiv, Bd. 91, 1883. E. E. S.]

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CHAPTER IV.

FEEDING EXPERIMENTS.

The observation frequently made that tuberculosis of the intestines is often associated with tuberculosis of the lungs, gave rise to the supposition that the tuberculosis occurring in the intestines was brought about by a kind of auto-infection, due to the swallowing of tuberculous sputa. It was from this point of view that most of the feeding experiments were undertaken.

*Klebs*¹ was the first, to my knowledge, who inaugurated experiments on this subject. He fed three guinea-pigs with grass, with which sputa from tuberculous individuals had been mixed, and afterward observed erosions on the lips, and enlargement of the lymphatic glands.

A year later *Aufrecht*² made very similar observations with rabbits. *Aufrecht* fed the animals with tuberculous substances from man. Post-mortem examinations revealed two small ulcers in the stomach, and numerous nodules on the peritoneum covering the liver. Microscopical examination of the nodules

¹ Virchow's Archiv, Bd. 44. 1868.

² Med. Centralblatt, 1869, No. 28.

showed a striking similarity between them and tubercles occurring in the serous membranes of man.

In 1870 *Klebs*¹ extended his investigations, and was able to corroborate his former results, his experiments being followed by positive success.

He fed guinea-pigs with tuberculous materials from man, and found, on post-mortem examination of the animals experimented upon, ulcers of the intestines, and nodules in the serous membranes. *Klebs* experimented successfully also with material from cattle suffering with murrain. Since *Klebs* had also observed that inoculations with human tubercles developed pearl-nodules in a calf, he declared, with *Villemin*, that murrain and tuberculosis were identical pathological processes, and of an infectious character.

*P. Gerlach*² fed animals with pearl-nodules, and with milk from cows affected with murrain, and found, on post-mortem examination, nodules in some cases in the lungs, in others in the serous membranes; from these investigations he emphasized the fact that the use of milk from such cows was dangerous.

Güenther and *Harms*³ boiled tuberculous materials from man before feeding them to the animals experimented upon, and no nodules developed themselves

¹ Zur Geschichte der Tuberculose. Virchow's Archiv, Bd. 49. 1870.

² Med. Centralblatt, 1871, No. 2.

³ L. c.

Tuberculous substances, however, from pigs, whether raw or cooked, produced an extensive production of nodules.

Another variation of these feeding experiments is found in the so-called *Dresden experiments*.¹ Two pigs were fed with mutton which had been made "tuberculous artificially." The animals experimented upon showed an extensive development of nodules after the lapse of five or six months.

*Chaveau*² arrived at positive results after feeding cattle and cats with tuberculous substances.

*Klebs*³ subsequently fed five guinea-pigs with milk from cows suffering from murrain. In four cases the results were positive, in only one negative. One animal only died. The others at first became emaciated, but soon recovered, and regained their usual strength, and it became necessary to kill them for examination. *Klebs*, in another series of experiments, first filtered milk from diseased cows, and then fed three guinea-pigs successfully with it. *Klebs* here, contrary to his former views, assumes that the virus of tuberculosis is soluble.

P. Bollinger,⁴ after feeding dogs with substances derived from cattle sick with murrain, obtained many

¹ Bericht über das Veterinärwesen in Königr. Sachsen, 1870-71, Citirt nach Boblinger.

² Recueil de Méd. vét., 1872, and Med. Centralblatt, 1874, No. 58.

³ Archiv, f. Experim. Pathologie. Bd. 1. 1873.

⁴ Archiv, f. Experim. Pathologie. Bd. 1. 1873.

negative results, the experiments on two sheep and two goats only producing results. Of the whole list of the above-mentioned observers who have made feeding experiments, *Bollinger* is the only one who felt the necessity of making counter-experiments. He, however, made but one counter-experiment. This was on a goat, with the contents of a splenic abscess occurring in a pig. The result was negative.

*Colin's*¹ experiments were all negative in their results. He firmly upholds, in accordance with the results of his inoculation experiments, the doctrine of the contagiousness of tuberculosis. He denies, however, the possibility of an infection from the intestinal canal, and explains the positive results obtained by feeding, by the supposition that the animals already had tubercles before the experiments were performed; or that, during the feeding, some particles of the food gained entrance into the trachea, and the infection of the animals took place from this source; or, he says, it might very easily have occurred that, during the feeding, which had often to be accomplished by force on account of the unusual food, a wound was accidentally made, through which the infection of the animals followed.

*Schreiber*² obtained the same negative results with

¹ Med. Centralblatt, 1873, No. 39. Compt. rend. 1873.

² Zur Lehre von der Artif. Tuberculose, Inaug. Dissert. Königsberg, 1875.

guinea-pigs and rabbits, using both boiled and fresh milk from cows afflicted with murrain.

*Tappeiner's*¹ experiments on dogs were followed partly by positive, partly by negative results. Nevertheless *Tappeiner* disputes the possibility of an infection from the intestinal canal and thinks that the animals became tuberculous, not as a result of feeding with the various infectious substances, but fell victims to an "inhalation tuberculosis," developed he thinks on account of the close proximity in which these animals were kept to the room in which he was conducting his inhalation experiments with tuberculous substances. *Tappeiner* holds that possibly the infected air gained access to the place in which the animals in question were kept.

*Oith*² fed rabbits with raw and cooked substances from cattle suffering from murrain. Both series of experiments were followed in some cases by positive, and in some by negative, results, the latter being the more frequent in feeding with cooked material.

Those rabbits which were fed with human tuberculous material, all remained healthy.

*Semmer*² made experiments on one hundred dogs, with pearl-nodules (from murrain). All were un-

¹ Virchow's Archiv, Bd. 74, 1878, and Deutsch Arch. f. Klin. Med. Bd. 29, 1881.

² Experim. Untersuchungen über die Fütterungstuberculose, Virch. Arch. Bd. 76. 1879.

³ Virchow's Archiv, Bd. 82. 1880.

cessful. *Semmer*, nevertheless, adheres to the doctrine of specificity, because, after inoculations with milk from cows with murrain. (subcutaneous or injected into the veins), nodules developed in pigs and sheep.

Semmer's statements were opposed by *Virchow*,¹ who considered it a great error for *Semmer* not to have made counter-experiments.

*Toussaint*² obtained positive results, by feeding rabbits with tuberculous beef or pork in a raw or badly cooked condition.

Sedemgrodsky,³ at the request of the Sanitary Commission of Saxony, made a series of experiments by feeding pigs and lambs with tuberculous substances, with cheesy degenerated portions of the human lung, with pearl-nodules, with milk, and with lung tubercles from cattle affected with murrain. The experiments with human tuberculous matter, were all negative. The use of milk led, it is true, to the development of nodules; but nodules of the same kind were found also in animals which had not partaken of milk from diseased cows. These experimenters therefore came to the following conclusion :

The assertion that the use of flesh or milk of cows affected with murrain produces tuberculosis in man, is without any positive foundation.

¹ *Virchow's Archiv*, Bd. 82. 1880.

² *Med. Centralblatt*, 1882. No. 8.

³ *Med. Centralblatt*. 1882. No. 31. Original article not available.

Finally, I must mention the investigations of *Putz*.¹ He found that the feeding of calves with human tuberculous material proved non-infectious.²

Large as the number of feeding experiments followed by negative results may have been, they prove nothing more than that in many animals, even if they eat tuberculous substances, no development of tubercles follows.

We must, therefore, turn our attention to the positive results, not because they indicate any thing concerning the question of the specificity of tuberculosis; for one thing is conclusively established, and that is, that the development of tubercles may be produced by the introduction of indifferent substances also. Besides, it has not been at all demonstrated as yet, as I have mentioned, whether a large number of other

¹ *Versammlung deutscher Naturforscher in Eisenach. 1882. Wiener Mediz. Blaetter, No, 41.*

² [*Schottelius* very recently opposed the identification of murrain with tuberculosis. He supports himself in his view by the anatomical differences of the two processes and by the reports of the Sanitary Commission (Prof. Reubold and Dr. Haecker) of the district surrounding Würzburg, Germany, in which district the sale of cattle affected with murrain has been permitted for fifteen years. The reports show that during this time no individual had received any noticeable injury from the use of the meat, and that persons who indulged heavily in its use were noted for their good and healthful appearance. *Virchow's Archiv, Bd. 91. 1883. E. E. S.*]

substances used in the same way as tuberculous materials for feeding, might not also lead to the development of tubercles. The positive results, however, arrived at by feeding, might be of the greatest value and importance in the theory of resorption. At present, however, the number of experiments made is too limited, and it has not been clearly shown whether they were entirely free from faults. It still remains to be determined, whether, during these forced feedings, injuries and unintended inoculations may not have been made; whether a confusion with entozoa-nodules has not arisen; whether animals with natural tubercles already developed may not have been used; and whether the development of the nodules did not take place as a consequence of the abnormal condition of the nutrition of the animals, produced by the peculiar process of feeding and food. The number of positive results, however, must be largely increased, and the manner of experimenting as well as the post-mortem appearances most carefully reported, before we can take these feeding experiments into consideration as a basis for the solution of these problems.

As a conclusion of this chapter, I would like to point out also that the reason for neglecting to make counter-experiments, might be found in the following considerations. It might be supposed that the feeding experiments did not need to be tested. All animals which take their usual food and are not tuber-

culous, might be regarded, one might suppose, as so many counter-experiments. This is not true, however. The accustomed food of these animals can not be considered in these experiments as the direct counterpart of feeding with tuberculous materials. Counter-experiments should certainly be made with food which the animals are not accustomed to eat, and somewhat analogous in its character to tuberculous materials—carcinomatous substances for instance. In cases of feeding with milk from cows diseased with murrain, the use of milk from healthy cows might be considered as a counterpart. It has, however, been seen that in the investigations made by order of the Sanitary Commission of Saxony, the use of both kinds of milk apparently produced tubercles. The whole question of infection by feeding seems still to require new and more careful experiments, in order to reach any satisfactory solution.¹

¹[It might, perhaps, not be out of place to mention here the latest views of *Klebs* that have just appeared in the last number of the "Real Encyclopedia," 1883. *Klebs* says: "To these observations (that the feeding of guinea-pigs with milk from tuberculous cows [murrain] developed tuberculosis in the animals experimented upon) many objections were raised, a thing to be expected in this age of skepticism, just as formerly the transmissibility of tuberculosis was disputed on all sides. The Bavarian government had inquiries made as to the question, whether the inhabitants of the country surrounding Würzburg, who partook of meat from tuberculous cattle, were more frequently attacked with tuberculosis than other individuals.

Notwithstanding the expected negative results, the referée, *Bollinger*, very praiseworthy held firmly to the idea founded on positive results, that the milk at least of tuberculous cows is to be regarded with suspicion. *Kirchow*, on the contrary, was of the opposite opinion, and thought that not even the milk of tuberculous cows would produce tuberculosis in man. I can not help calling attention to the want of logic in coming to these conclusions, taking into account the great importance which the question possesses from a practical standpoint. How often do we see that the causative influence of organisms, when brought into contact with the human body, does not, under all circumstances, produce the disease which it otherwise is capable of developing. It is, furthermore, an often-corroborated fact, that those individuals, who are constantly employed with and surrounded by certain injurious organisms, become less susceptible to these injurious influences, acquiring a certain immunity against them. It has never been settled, and the question not even looked into, whether those inhabitants, referred to above, have not learned by experience, to adopt certain precautions, in order to prevent deleterious results; perhaps they carefully remove the tubercle-nodules from the meat or subject the parts to a thorough and prolonged cooking. It is certainly to be lamented that the decision of a question of such great fundamental importance to the welfare of the public, is treated so lightly." E. E. S.]

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CHAPTER V.

EXPERIMENTS WITH "PURE TUBERCLE-VIRUS."

After the experiments of *Villemin*, an eager and animated discussion arose among the adherents to the doctrine of specificity as to the nature of the supposed tubercle-virus. The adherents of this theory, in order to account for the fact that very small quantities of tuberculous material were sufficient to infect an animal, and that the product of this inoculation might again be successfully transferred to other animals, supposed the existence of a contagium animatum.

This supposition gained seeming strength from the investigations of *Buhl*.¹

Buhl reported that in the cheesy centers, as well as in the giant-cells of tubercles,² the existence of microorganisms (globular and rod-shaped) might be demonstrated. At the same time *Buhl* gave his opinion that these bacteria might constitute the "materia peccans" of tuberculosis.

The theory of a contagium animatum had already

¹ Lungenentzündung, Tuberculose und Schwindsucht, 1873.

² He refers to true tubercles of man, and not to tubercles produced by inoculation with which *Grohé* experimented.

been opposed by *Waldenburg*. *Waldenburg* called attention to the fact that this theory rested simply upon experiments which did not necessarily point to the existence of such a virus. He was not able to corroborate the microscopical discovery by *Buhl* of the presence of bacteria in tubercles and cheesy centers, nor did he attach much weight to *Buhl's* reports.

*Friedlaender*¹ declared that the granules in giant-cells were soluble in caustic potash, and consequently could not be micrococci.

A careful test of the reports of *Buhl* was made by *A. Wolff*² also. *Wolff* used lenses of high powers, and all the then known precautions. His experiments deserve attention, especially because they were made upon the omentum, the most favorable of all membranes for examination. *Wolff* was unable to corroborate the statements of *Buhl*, and closes his histological investigations with the words: "Although, so far, I have not been able to find bacteria in giant-cells and recent tubercles, nevertheless, if, at some future time, I should find tubercles that contained bacteria, I would not hesitate—if one is not inclined to accept two forms of tubercles, those without and those with micrococci—to regard the development of micrococci in the last as an accidental accompaniment."

This was the situation when *Klebs*,³ in the year

¹ Volkmann's Sammlung Klinischer Vortraege. No. 64.

² L. c.

³ Prager Med. Wochenschrift, 1877. No. 42 und 43.

1877, appeared in a series of new investigations—investigations by which the theory of a contagium animatum was indisputably proved.

Klebs declared that he had produced bacteria¹ of tuberculosis isolated, and had, by inoculating them, made the animals inoculated tuberculous.

Klebs first placed the white of fresh eggs in vessels that had been thoroughly cleansed, and were protected from dust by cotton. After he had demonstrated, by a long period of observation, the absence of every trace of decomposition, tuberculous material was introduced. On the second or third day the culture-fluid showed a perceptible cloudiness, which the microscope demonstrated to be due to the presence of a large number of small moving granules, and some objects having the appearance of short rods. Small quantities of this clouded fluid were now put into another clean vessel filled with albumen, and this, too, soon became cloudy. *Klebs* now put a single drop of this fluid into fresh albumen; and, in this way, he cultivated the bacteria through many generations.

Small quantities of these culture-fluids, injected into the peritoneal cavity of healthy animals, led, as *Klebs* reports, to the development of numerous nodules as if genuine tuberculous materials had been

¹ *Klebs* by this implicitly says, that the tubercle-virus is not soluble in water, and thus, for the third time, changes his opinion concerning the solubility of the poison in question.

inoculated. *Klebs*, furthermore, examined these nodules microscopically, and found in them organisms similar to those contained in the inoculated culture-fluid. www.libtool.com.cn

{ From these experiments *Klebs* concluded that the deposit and multiplication of the cultivated organisms precedes tuberculous cell-proliferation in those places where tubercles develop later, and that, therefore, the organisms are the primary cause of tuberculosis. For this reason *Klebs* has given to the organisms cultivated by him the name of "monas tuberculosum."

The experiments of *Klebs* were soon after repeated by *Schueller*¹ with similar success. *Schueller* also extended the culture experiments so as to include scrofulous and lupous materials. He declared that the organisms cultivated from the above-named materials were indetical with the monas tuberculosum of *Klebs*, and, like this, produced tuberculosis. Thus, *Schueller* concludes that tuberculosis, scrofulosis, and lupus, must be regarded as identical processes of disease.

Schueller also made a few counter-experiments with inoculations or injections into the joints of bacteria of putrefaction, alcohol, and India ink, without, in any case, leading to the development of nodules.

¹ Ueber Therapeutische Versuche. Archiv, für Experim. Pathologie. Bd. XI. 1879, and Exp. und Histolog. Untersuchungen über die Entstehung der Tuberculose, etc. 1880.

After *Schueller* had, in this manner, satisfied himself of the transmissibility of tuberculosis, he made a series of therapeutical experiments on the animals thus artificially infected. He either made them inhale benzoated soda or injected pilocarpin subcutaneously. In consequence of these measures, an improvement, more or less marked, of the greatly debilitated condition of the animals is said to have taken place.

*Reinstadler*¹ also confirmed the conclusions of *Klebs*. He inoculated rabbits with fluids, the results of a third cultivation. The result was positive in each case. Inoculations, also, with culture-fluids that had been supplied with material from scrofulous lymphatic glands were followed by like results.

*Deutschmann*² also reported investigations by which he thought to strengthen the theory of *Klebs*.

Deutschmann injected fluids which contained monas tuberculosum into the aqueous chamber of the eyes of rabbits—the fluids used being serum or sediment from tuberculous pus, aqueous humor from a rabbit's eye in the iris of which nodules had been produced by the injection of tuberculous material into the aqueous chamber, and finally aqueous humor from the eye of a child affected with tuberculosis of the iris.³ *Deutschmann* found positive results in those

¹Archiv für experim. Pathologie, Bd. XI., 1879.

²Med. Centralblatt, No. 18, 1881.

³[This has only lately been recognized as a distinct disease,

cases only where the sediment or the aqueous humor that contained cheesy particles had been inoculated. In all other cases the inoculations proved failures.

From these observations, *Deutschmann* supposes that the *monas tuberculosum* is the cause of tuberculosis, but that the organisms must be inoculated with solid particles at the same time; without these latter, he thinks, the absorption of the monads takes place too rapidly, and in consequence they can not act so effectually.

Finally inoculations and inhalations with culture-fluids have been made by *Toussaint*¹ and *Weichselbaum*.²

Weichselbaum experimented with inhalations of culture-fluids made with tuberculous materials and produced nodules, but few in number (two to nine). Solutions, however, rendered sterile by boiling or by the addition of bi-chloride of mercury, constantly gave negative results.

The theory of *Klebs*, therefore, would seem to be sufficiently upheld and fortified by a series of experiments. This seemingly strong position of *Klebs's* theory lasts only so long, however, as we consider it the tubercles developed being considered as histologically the same as granuloma. *Haab* regards them as the local manifestation of a general miliary tuberculosis. The question of the true nature of the tubercle-like nodules in the iris is, however, still unsettled. E. E. S.]

¹ L. c.

² L. c.

aside from the history of inoculation experiments. As soon as we contrast his theory with the results of the inoculation experiments of other observers, the matter assumes a different aspect.

The more earnestly *Klebs* advocates in his reports, the specificity of tuberculosis, the less attention does he give the work of his predecessors. In his first investigation, *Klebs* agrees that indifferent substances may develop nodules and disputes only that these nodules are true tubercles. In his next series of investigations and articles he advances a step. He doubts that nodules may be developed by indifferent substances at all. In his last publication, in which the discovery of the *monas tuberculosum* is reported, the inoculation experiments with indifferent substances are entirely ignored; and yet a criticism of *Klebs's* theory is only possible by taking into consideration the records of these inoculation experiments.

Klebs, as has already been mentioned, brought forward three points in favor of his theory, viz: 1. Peculiar bacteria may be cultivated from tuberculous substances. 2. These bacteria, on being introduced by inoculation, cause tuberculosis to develop in animals. 3. Bacteria, which are identical with cultivated ones, are found in nodules produced by inoculation and in human tubercles.

Against these statements the following considerations may be brought forward:

1. *Klebs* declared that he had cultivated a peculiar,

and until that time unknown, micrococcus. He had experimented as was described before, by using solutions of albumen and particles of a tuberculous lung. *Klebs* undertook these culture experiments with the theory that the tuberculous substances which he had brought into contact with his culture-fluids were made up of a peculiar tissue and the bacteria about to be cultivated. The tissue, *Klebs* thought would be removed by the long-continued cultivation, and, therefore, only the bacteria be left in the vessels containing the later broods and generations.

This theory is, however, entirely illogical, for it is certainly equally possible that other bacteria might also be present in the tuberculous particles of lung. It was shown by *Tiegel*,¹ by numerous experiments, that various organs of perfectly healthy animals contained bacteria of decomposition. Why, then, could not these same bacteria be present in a tuberculous lung, taken from a cadaver?

Klebs should have proved in the first place that the organisms of decomposition were entirely absent in the tuberculous lung, and especially so since the bacteria cultivated by him were in no way to be distinguished from the bacteria occurring during putrefaction. *Klebs* has simply taken it for granted that the bacteria originating from tuberculous lungs, are the monas tuberculosum.

2. *Klebs* declares himself to have proved that inoc-

² Ueber Coccobacteria septica. Virch. Archiv, Bd. 60, 1874.

ulations with monas tuberculosum, will make the animals inoculated tuberculous. But this again is only an unproved assertion. *Klebs* probably forgot that his predecessors had obtained similar results with bacteria of decomposition and spores of micro-organisms, and even with carmine and cinnabar.

3. The third statement, too, has its weak points. He declares that inoculation nodules and human tubercles contain the monas tuberculosum.

The presence of the monas tuberculosum does not prove much. I have already shown that after inoculations with carmine the nodules contained carmine; after inoculation with micrococci, threads of micro-organisms. Why should not the nodules produced after inoculation with the bacteria cultivated by *Klebs* also contain bacteria?

The experiments of *Klebs* are more difficult to test than are those of his predecessors. The presence of a granule of cinnabar in a tubercle, is certainly more easily demonstrated than that of a colorless granule; the latter is very difficult to distinguish from the granules of the cells. Moreover, the methods of staining bacteria were not so well developed at that time as they are now.

Klebs furthermore argues that human tubercles also contain the monas tuberculosum. But if *Klebs* based his far-reaching theories upon the fact that he discovered the monas tuberculosum in tubercles, he has certainly sought refuge on ground upon which it is

most difficult to oppose him; for who would dare to affirm to the contrary? It is, however, just as difficult on such ground to bring forward proofs and awaken confidence in the conclusions reached.¹

After these remarks very little remains to be said of the work of those experimenters who made their investigations under the bias of *Kleb's* theory. I

¹ [In the last number of the "Real Encyclopedia," 1883, *Klebs* thus defines tuberculosis: Tuberculosis is a specific infectious disease, caused by a peculiar kind of low organisms belonging to the class of "*spalt-pilze*." The symptoms of the disease depend, in the first place, upon the point of entrance of these organisms and the manner of their distribution from this point; in the second place, upon the reaction taking place in the tissues, which follows in all the regions in which the infecting organisms implant themselves and multiply. The anatomical form of tubercle-nodules depends upon the formation of isolated colonies of these organisms; in places where the extension of these is more general, diffuse inflammations may develop in consequence of the reactive tissue changes. The tissue elements which are developed in these pathological products have no specific significance, as their peculiar form, etc., is dependent only upon the course of the local process. The sequestration of these tubercle organisms, in the local foci, brings about the long pauses taking place in the course of the disease, while the renewal of the vegetative process causes fresh outbreaks. The death of the organisms finally leads to a complete cessation of the process; but the resulting effects in the organs, especially extensive destruction of their tissues, may cause serious incurable structural changes, and may also produce suitable soil for the appearance and development of other processes, septic ones, for instance. E. E. S.]

mention only that the statement of *Schueller* of the presence of the monas tuberculosum in lupous skin, and its successful inoculation, is evidence rather against, than for the correctness of *Klebs's* view. Inoculations with lupous skin are certainly nothing more than counter-experiments, which argue against the specific character of tuberculosis.

I would like to emphasize this fact, the more because *Schueller* states that those investigations which he regarded as counter-experiments were unsuccessful.

This latter statement itself, it seems however is not entirely correct. *Schueller* mentions that, of the animals used for counter-experiments, only those did not become tuberculous which were separated from the tuberculous ones; those that remained with the animals affected by tuberculosis produced by inoculation, were infected and developed tuberculosis. From this remark it follows that in *Schueller's* experiments also, the animals which had been inoculated with non-tuberculous substances became tuberculous; but whether on account of their living together with sick animals or not he has not proved.

A few more remarks will be added regarding the investigations of *Deutschmann*. *Deutschmann*, as shown above, interpreted the results of his experiments in favor of *Klebs's* theory. In truth, however, *Deutschmann* reports that he found that fluids which contained only the monas tuberculosum are not *inoculable*, but become so as soon as they contain, beside the

bacteria, cheesy particles. These results give *Deutschmann* cause for declaring that the monas tuberculosum is the tubercle-virus, and that cheesy particles are not capable of producing tubercles. In passing, I would like to call attention again, in this connection, to the fact that the history of inoculation experiments teaches that it was especially to the cheesy particles that the development of tubercles was most generally attributed.

I have nothing to say of the cultivation experiments of *Weichselbaum*, since that author himself declares them not free from objections.

The theory of *Klebs* led to a series of histological examinations in addition to the above-mentioned experimental investigations.

*Rindfleisch*¹ maintained that the granulation of the giant-cells of tubercles was due to zoöglea (cocci). Positive proofs were not, however, brought forward by *Rindfleisch*. He simply says: "At first, I thought this (the granulation of the giant-cells) coagulated lymph; but now, however, I would have no objection on account of the sameness of these granules, if some one were to consider them a development of a mass of micro-organisms."

That the resemblance of the granules does not prove what *Rindfleisch* endeavored to prove by it, is evident. Many precipitates, both inside and outside of the cells, are composed frequently of granules of the same

¹ Tuberculose. Virchow's Archiv, Bd. 85. 1881.

size and form, and, for this reason, are not micro-organisms. The statement of *Rindfleisch* can not therefore be taken into consideration in determining the question whether vegetations of micro-organisms occur in tubercles or not.

Almost simultaneously with *Rindfleisch*, *Aufrecht*¹ reported that the centers of nodules (produced by inoculating rabbits with substances infected with murrain) were not composed, as was most generally supposed, of necrotic cells, but of micrococci and rod-shaped bacteria. The long diameter of these organisms was one and one-half times the transverse diameter.

Soon after *Baumgarten*² saw rod-shaped bacteria in similar nodules. He, however, regarded them as entirely different from those which *Aufrecht* described. The bacteria found by *Baumgarten* are three, even five and six, times as long as they are broad. They are present in every nodule following inoculation. Cocci and diplococci, contrary to *Aufrecht's* theory, *Baumgarten* never observed.

Bacteria of the same kind were afterward observed by *Baumgarten* in human tubercles also.

From the foregoing it will be seen that these histological investigations are not favorable to the theory of *Klebs* of the constant presence of the *monas tuberculosum* in artificially-produced nodules, and in

¹ Pathologische Mittheilung. Magdeburg, 1881.

² Med. Centralblatt, 1882. No. 15.

human tubercles: *Aufrecht* as well as *Baumgarten* reports the occurrence of rod-shaped bacteria; and while *Aufrecht* makes mention of cocci also, *Baumgarten* completely denies their presence.

[Such was the condition of things when *Robert Koch* published his investigations on the etiology of tuberculosis, to which, considering their importance, the next chapter will be devoted. E. E. S.]

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CHAPTER VI.

KOCH'S EXPERIMENTS.

In March, 1882, the whole medical world was greatly aroused by the appearance of an article that had been read before the Berlin Physiological Society by *Robert Koch*, under the modest title of "The Etiology of Tuberculosis."¹ *Koch* had already distinguished himself by numerous experiments on splenic fever, and had devised new methods for staining the micro-organisms of disease. These achievements had given him a high standing both among microscopists and mycologists.

For three months *Koch* had busied himself most diligently seeking the primary cause of tuberculosis, making it his aim to discover, if possible, minute organisms which might perhaps be the cause of the disease. The experiments of preceding investigators had, indeed, made it probable that the cause of tuberculosis might be found in microscopically minute organisms. In view of the results that had been obtained by other experimenters with other diseases, and in view of the great progress that medical science was making in these modern times, *Koch* was certainly

¹ Die Etiologie der Tuberculose. Berliner Klin. Wochenschrift. 1882. No. 15.

perfectly justifiable in starting out with this idea, and directing his endeavors in this channel.

The work and purpose being thus determined, it was only necessary to devise ways and means for rendering the supposed schizomycetes visible under the microscope, and for proving indisputably, after they had been rendered visible, that they were in reality the *specific* cause of tuberculosis. Master as *Koch* was in the various methods of staining, it did not take him long to find a suitable plan; in fact he adopted a method which he had already used in his experiments on the micro-organisms of splenic fever, and which he had then found most efficient in staining these organisms.

The method is as follows: The materials to be examined are prepared in the way usually adopted for the examination of pathogenic bacteria; they are either heated and dried on a cover-glass, or sections are made of them after they have been hardened in alcohol. The cover-glass, or the sections, is then transferred to a staining fluid that has been prepared by mixing 200 c.cm. distilled water with 1 c.cm. of a concentrated alcoholic solution of methylene blue, and 0.2 c.cm. of a ten per cent. caustic potash solution are added. The objects to be stained remain twenty to twenty-four hours in this fluid; however, by heating this coloring fluid to 40°C. in a water-bath, the process can be shortened to one-half to one hour. The cover-glasses are then treated with a concen-

trated aqueous solution of vesuvin (which is to be filtered every time that it is used), and are then washed with distilled water for one or two minutes. Under the microscope the bacilli of tuberculosis now show themselves stained blue, while all the other constituents of the animal tissues, and especially the nuclei of the cells, are colored brown. All other bacteria so far examined by *Koch*, with the exception of the bacillus leprae, assume a brownish color on being treated with this coloring method. The sections are treated in almost the same way. They are transferred to the solution of vesuvin, in which they remain fifteen to twenty minutes, and are then washed with distilled water until the blue color has disappeared, and a more or less intense brown color remains. The sections are then placed in alcohol, clarified with oil of cloves, and may be examined either in this fluid or transferred to Canada balsam. Other aniline dyes may also be used in the same way, but the staining is not as marked as with methylene blue.

In this way *Koch* was enabled to see that which hosts of other observers had for many years vainly endeavored to discover.

The bacteria thus found exhibited various peculiar characteristics. They had a rod-shaped form, and belonged, therefore, to the group of bacilli; they were very thin, and about one-quarter to one-half as long (in some cases reaching the entire length) as the diameter of a red blood-corpuscle. They

possessed, as regards size and form, a striking similarity to the bacilli leprae, the latter being distinguished from them, however, by being somewhat more slender and pointed at the ends; the bacilli leprae, also, become stained, when treated according to the staining method of *Weigert*, while the bacilli of tuberculosis do not.

Koch found that the bacilli discovered by him were present in large numbers, in those places where the tuberculous process was just beginning or was progressing very rapidly; they are then crowded together closely in small groups, sometimes in the form of bundles. They are found mostly in the interior of the cells, but may also, especially at the margins of large cheesy centers, be found in groups not in the interior of the cells. After tubercles become fully developed and degeneration sets in, the bacilli become less in number—being found only in small groups, or isolated, along the margins of the tubercle-centers, and side by side with bacilli very faintly colored, which latter are probably either just on the point of death or already dead. If giant-cells are present, the bacilli are generally found in the center of these cells, the bacilli acting probably as foreign bodies around which the giant-cells are developed.

The bacilli may also be examined, without being stained, by the addition of a drop of distilled water; or better still, serum of blood. They appear as very

fine rods, which possess only molecular movement, and have no motion of their own.

Koch now made a series of examinations of tuberculous matter of man and animals to detect the presence of bacilli. Of human subjects he examined eleven cases of miliary tuberculosis, twelve cases of cheesy bronchitis and pneumonia, one case of a solitary tubercle found in the brain, two cases of tuberculosis of the intestines, three cases of freshly extirpated scrofulous glands, and four cases of fungoid inflammation of joints. He found that the bacilli were never wanting in the miliary tubercles of the lungs. They were also demonstrated to be present in miliary tubercles of the spleen, the liver, and the kidneys, and were discovered in large numbers in the gray nodules of the pia-mater in cases of meningitis basilaris. The caseated bronchial glands also contained swarms of bacilli. In the twelve cases of caseous bronchitis and pneumonia, the presence of the bacilli was generally limited to the margins of the cheesy infiltrated tissues, but they were present here in large numbers. Sometimes bacilli were found in the interior of the infiltrated lung tissue also. In most of the lung cavities the bacilli were very numerous. In the larger cavities they occurred in connection with other bacteria, but were easily separated and distinguished from these by the staining method detailed above—the bacilli of tuberculosis being colored blue, the other bacteria brown. In the cases of tuberculosis of the

intestines the bacilli were also very easily demonstrated, especially in the smaller most recent nodules. In the mesenteric glands of the cases examined, the bacilli were also found. In only two of the three scrofulous glands examined, were bacilli, inclosed in giant-cells, visible; and of the four cases of fungoid inflammation of the joints, bacilli in small numbers were found in two only.

Of animals, *Koch* examined ten cases of murrain with calcareous degenerated nodules in the lungs, the peritoneum, and the pericardium. In every case bacilli were found, and especially in the interior of the giant-cells of the tissue immediately surrounding the calcareous nodules. From one to twenty bacilli were found generally in each giant-cell. In a cheesy lymphatic gland from the neck of a pig, bacilli were also present, and in the organs of a chicken bacilli were found, both in the tubercle-nodules of the marrow of the bones, and also in the peculiar large nodules of the intestines, the liver, and the lungs. In three monkeys that had died from tuberculosis, bacilli were observed in the numerous nodules of the lungs, the spleen, the liver, the omentum, and in the caseous glands. Nine guinea-pigs and seven rabbits that were affected with tuberculosis, were also examined and bacilli demonstrated in every case.

Besides these cases of spontaneous tuberculosis, a large number of animals (one hundred and seventy-two guinea-pigs, thirty-two rabbits, and five cats)

that had been infected by inoculations with tuberculous substances (gray and cheesy tubercles from the human lung, sputa of phthisical persons, etc.) also came under examination. The tubercle-nodules of the lungs were generally investigated, and in not a single case were bacilli absent.

From these numerous observations, *Koch* came to believe it proved, that in all tuberculous affections of man and animals the bacilli discovered by him, so different from all other known bacteria, were constantly present. "It does not follow, however," says *Koch*, "that the bacilli thus found are the cause, the starting-point of tuberculosis; although the fact that the bacilli are found in those points especially where the tuberculous process is just beginning or is progressing rapidly and disappear when the diseased process ceases, rather favors this supposition." In order to prove and substantiate the supposition that tuberculosis was due to the entrance of bacilli, and to their growth and multiplication, it became *Koch's* task to isolate the bacilli from the body, to cultivate them through many generations, purifying them completely from every particle of diseased product or tissue, and finally to transfer these purified isolated bacilli to animals, and to note whether tuberculosis showed itself in consequence, as with inoculations of tuberculous products generally. In this way he endeavored to prove, beyond doubt, that the bacilli themselves,

and not other diseased products, were the actual cause of the disease, and that tuberculosis is therefore a specific infectious disease.

We shall see how *Koch* went about this. He prepared first a firm, transparent, nutritive soil, upon which the parasites could be sown, and which remained firm even at the temperature required for brooding. Serum from the blood of cattle or sheep, as pure as possible, is placed in a test-tube closed by a cotton wad, and heated daily for six days, an hour at a time to 58°C . This proceeding generally succeeds—not always, however—in rendering the serum sterile. It is then heated for several hours to a temperature of 65°C . until it congeals, when it appears as an amber-colored, perfectly transparent, or slightly opalescent, jelly-like mass, which should not show the least development of bacteria when kept for several days at the temperature required for brooding. If it is heated beyond 75°C . it soon becomes opaque. In order to have as large a surface as possible upon which to cultivate the bacilli, the test-tube should be made to stand in a slanting position while the serum congeals. If direct microscopical examinations are to be made, the serum is allowed to congeal on watch crystals, or other small hollow glass dishes, such as are found in every histological laboratory.

The tuberculous substances are now transferred to this nutritive stratum of congealed blood-serum in

the following way: Every precaution possible for a thorough disinfection of every instrument used must be taken. All instruments are heated red-hot just before use. As quickly as possible, a small speck of tuberculous matter from the lung or elsewhere is removed with a previously-heated platinum wire to the surface of the congealed blood-serum in the test-tube. Care must be taken to do all this in as short a space of time as possible and especially not to open the test-tube more than necessary. Six to eight test-tubes are treated in the same way, since, no matter how careful the operator may be, foreign impurities will now and then gain access.

The test-tubes thus treated are now placed in a brooding apparatus and kept continually at a temperature of 37° to 38° C. No perceptible change will be observed in the first week; if bacteria do develop in the first few days and multiply rapidly, the experiment must be considered a failure, as these are due to the presence of foreign impurities. The bacilli of tuberculosis generally become visible to the naked eye in the second week, about the tenth day, showing themselves as very minute points and dry scaly-like particles which generally surround the tuberculous matter introduced. With the aid of a weak magnifying power of thirty to forty diameters, the bacilli colonies may be seen at the end of the first week. They appear as very delicate spindle- and generally S-shaped structures, which, if stained and treated in the

way described, and then examined with a high magnifying power, are seen to be composed of the bacilli described above. The growth and multiplication of these colonies proceed, ~~with the course of~~ three to four weeks, up to a certain degree; they become larger but scarcely ever reach the size of a poppy-seed. The slow growth, the peculiar dry, scaly, and firm character of these bacilli colonies, are not found in any other kind of known bacilli; thus a differentiation can be made easily and no confusion need arise. The growth of the colonies is ended in a few weeks and probably no enlargement takes place from this time, for the reason that the bacilli are entirely without motion of their own. In order to cultivate the bacilli through many generations, it is necessary to transfer them after ten to fourteen days to a fresh nutritive soil, this being accomplished by means of a platinum wire previously heated red-hot. In this way the bacilli can be cultivated through generation after generation extending even over a half year.

Koch now made inoculation experiments with the cultivated bacilli and other substances. The importance of the question and the results which were obtained by other experimenters, all demand a somewhat detailed account of these experiments. In making these experiments every known precaution was employed by disinfecting the point of inoculation, heating the instruments before using, etc. Four to six guinea-pigs were inoculated at a time with the sub-

stance, the virulency of which was to be tested. The success was constant; in all the animals inoculated with fresh materials containing the bacilli of tuberculosis, the wound generally closed on the following day, remaining unchanged for about eight days, when a nodule developed which either increased in size without breaking or more frequently changed into a shallow ulcer. Two weeks after the inoculation, the inguinal glands on the side inoculated became enlarged to the size of peas; sometimes, though much less frequently, the axillary glands also participated and became swollen. From this time on the animals lost weight rapidly, and either died in four or five weeks or were killed in order to exclude the possibility of a combination with a spontaneous tuberculosis. In the organs of all these animals, and especially in the spleen and the liver, the characteristic, well-known tuberculous changes were found. That the infection of the guinea-pigs was brought about only by the inoculated substances, is evident from the fact that in inoculations of other animals at the same time with the contents of a scrofulous gland, fungoid masses from a joint—in both cases no bacilli being present—and finally inoculations with tubercles of the lung of a monkey, some of which tubercles had been dried for two months, while some had been preserved in alcohol for one month, not one single animal became infected. All those that had been inoculated with substances containing bacilli

were affected with tuberculosis in a high degree after the lapse of only four weeks. Bacilli were also again cultivated from the tuberculous materials of the inoculated ~~wife infected animals~~ and from these exactly similar results were secured.

Koch had now shown by his investigations the constant occurrence of characteristic bacilli in tuberculosis, and had demonstrated that these bacilli could be derived from tuberculous organs and isolated and purified by means of cultivation. The important question, however, remained to be answered whether the isolated bacilli, if again introduced into the body, would produce the pathological process of tuberculosis. I will recount somewhat fully the different experiments instituted.

1st Experiment. Of six guinea-pigs that were kept in one and the same cage, four were inoculated in the abdomen with culture-bacilli derived from human miliary tubercles of the lungs, that had been cultivated for fifty-four days through five generations. The remaining two pigs were not inoculated. Fourteen days after the inoculation, the inguinal glands of the animals inoculated became swollen, the inoculation wound became ulcerated, and the animals lost flesh. One of the animals inoculated died thirty-two days after the inoculation; the rest were killed on the thirty-fifth day. The guinea-pigs that had been inoculated showed extensive tuberculosis of the spleen, the liver, and the lungs; the inguinal glands were

much swollen and caseated, the bronchial glands but slightly so. The two animals that had not been inoculated showed not the least trace of tuberculosis either in the lungs, the liver, or the spleen.

2d Experiment. Of eight guinea-pigs six were inoculated with culture-bacilli coming from the tuberculous lung of a monkey, and having passed through eight generations in ninety-five days. Two animals were not inoculated. Result same as in *Exp. 1*. The six animals inoculated were found tuberculous in a high degree; the two not inoculated, perfectly healthy.

3d Experiment. Of six guinea-pigs five were inoculated with culture-bacilli from the tuberculous lung of a cow. The five animals inoculated were found to be tuberculous on post-mortem examination, while the one not inoculated was found to be perfectly sound.

4th Experiment. A number of animals (mice, rats, hedgehogs, pigeons, frogs, and a hamster), of the susceptibility of which to tuberculosis nothing was as yet known, were inoculated with culture-bacilli, the bacilli having been cultivated for one hundred and thirteen days. Four mice were killed fifty-three days after the inoculation, and numerous tubercle-nodules were found in the spleen, the liver, and the lungs; similar results were found in the hamster, killed on the fifty-third day.

These four experiments showed that inoculations in the abdomen of animals with culture-bacilli

produced the same changes as if fresh tuberculous substances had been used. In the next following experiments the inoculations were made into the aqueous chamber of the eyes of rabbits, in order to learn whether, in this modified procedure, the artificially-cultivated tubercle-virus would have the same effect as the natural.

5th Experiment. Three rabbits received a small speck of culture-bacilli in the aqueous chamber of the eye. A few days after a severe iritis set in, and the cornea became cloudy and of a yellowish-gray color. The animals rapidly became emaciated. They were killed twenty-five days after the inoculations, and numerous tubercle-nodules were found scattered throughout the lungs.

6th Experiment. Of three rabbits, one received an injection of pure blood-serum into the aqueous chamber of the eye, the other two injections of this serum in which small specks of culture-bacilli had been introduced. In the two last-mentioned cases the same results as in the preceding experiment took place. The one that had been injected with pure blood-serum remained perfectly sound.

7th Experiment. Of four rabbits, one received pure blood-serum into the aqueous chamber of the eye, the second a minimum of the same serum containing a speck of culture-bacilli, and the third and fourth received a larger quantity—several drops—of the same fluid as the second rabbit. Iritis, panophthal-

mitis and rapid emaciation, soon developed in the last two rabbits. In the second rabbit the eye at first remained unchanged, but, at the end of the second week, a few yellowish-white nodules developed on the iris, and soon a regular tuberculosis of the iris followed. Fresh nodules appeared continually; the cornea gradually became more and more opaque, and the iris at length disappeared from view. Thirty days after the inoculation the animals were killed. The first was found perfectly healthy; in the second, besides the changes in the iris already mentioned, the lymphatic glands, near the jaw and ear, were swollen, and the lungs and other organs were still free from tubercles; in the last two rabbits innumerable tubercles were scattered throughout the lungs.

8th Experiment. Six rabbits were inoculated in the aqueous chamber of the eye with culture-bacilli derived from human miliary tubercles of the lungs, cultivated for one hundred and five days. All six animals developed tuberculosis of the iris; in some also an infiltration of the conjunctiva with tubercle-nodules took place.

Koch, however, did not rest here, but still prosecuted his experiments, inoculating animals with culture-bacilli in the abdomen, or he introduced it directly into the circulation, and finally endeavored, also, to make those animals, which were not easily infected, tuberculous by using the artificially-cultivated tuberculous matter.

9th Experiment. Of twelve guinea-pigs, ten were treated with injections into the peritoneal cavity, of blood-serum into which a speck of culture-bacilli had been introduced; the eleventh was injected in the same place with pure blood-serum, and the twelfth, which had a recent wound in the abdomen, was not touched at all. Of the animals that had received injections five died, one each on the tenth, thirteenth, sixteenth, seventeenth, and eighteenth days. The remaining pigs were killed on the twenty-fifth day. Post-mortem examinations of the first five showed a thickening and infiltration of the omentum with a firm, yellowish-white mass; microscopical examination showed this mass to be made up of innumerable tubercle-bacilli. The animals that were killed also presented development of tubercles in the spleen and the liver. The eleventh and twelfth animals were found perfectly sound.

10th Experiment. A number of white rats were fed for two months almost exclusively with portions of dead bodies of tuberculous animals. From time to time, a rat was killed and examined. In a few cases isolated small gray nodules were found in the lungs; the majority, however, remained perfectly healthy. Inoculations with tuberculous substances, and with culture-bacilli, had no effect on the animals, although they were repeatedly made. After the rats had been fed with tuberculous substances for several weeks, five of them received injections into

the peritoneal cavity, of small portions of culture-bacilli; five weeks later these were killed and tubercle-nodules were found in the lungs, and in the greatly-enlarged spleen. This experiment shows that rats, otherwise unaffected by infectious materials generally, if inoculated with culture-bacilli, may become tuberculous. It must be remembered, however, that feeding with tuberculous substances preceded the inoculation.

11th Experiment. Of twelve rabbits, two received injections of a half c. cm. of pure blood-serum into the auricular vein. Ten rabbits received injections in the same way with blood serum and culture-bacilli that had gone through various generations. The first two rabbits remained perfectly well; all the rest rapidly became emaciated and began to breathe with difficulty in the second week. They soon began to die, one on the eighteenth day, two on the nineteenth day, and so on. Two were killed on the thirty-eighth day after the injection. In all the animals numerous miliary tubercles of the lungs were found; the liver and the spleen, too, of all these animals, contained many tubercles. The first two rabbits were found normal.

12th Experiment. Two large healthy cats received injections with blood-serum mixed with culture-bacilli, into the cavity of the peritoneum. One cat died nineteen days afterward. The omentum was infiltrated with a whitish mass, and was, in places, one cm.

thick; the spleen was enlarged; a macroscopical development of tubercles had not yet taken place, but, microscopically, numerous tubercles were found in the lungs, the liver, and the spleen. The second cat was killed on the forty-third day and tubercles were found in the lungs, the spleen, and the omentum—very few in the liver.

13th Experiment. A bitch received an injection of two c. cm. of blood-serum, mixed with culture-bacilli, into the peritoneal cavity. No change was perceptible for the first two weeks; gradually, however, she became less frisky, lost appetite, and, at the end of the third week, a perceptible swelling of the abdomen developed. She was killed in the beginning of the fifth week. Post-mortem examination showed a clear, straw-colored fluid in the abdominal cavity. The omentum, the mesentery, the surface of the intestines and the bladder, were studded with tubercle-nodules; the spleen, the liver, and the lungs, also contained innumerable miliary tubercles.

From these experiments it will be seen, that all the animals experimented upon—whether they were inoculated with culture-bacilli in the subcutaneous cellular tissue, or received injections into the peritoneal cavity, or into the aqueous chamber of the eye, or directly into the circulation—without a single exception, became tuberculous, with nodules present, not alone in a single place or organ, but scattered throughout

the organs of the body, depending on the amount of the infectious material introduced.

All these facts taken together, led *Koch* to assert that the bacilli occurring in tuberculous substances were not merely the attendants of tuberculous processes but the cause of them, and that the bacilli actually represented the *true tubercle-virus*. He, furthermore, added that henceforth it would not be difficult to decide what is tuberculosis and what not. Not the peculiar structure of tubercles, not their want of blood-vessels, not the presence of giant-cells, will decide the question; but the proof of the presence of the tubercle-bacillus. With this as a criterion, he pronounced, in accordance with his observations, miliary tuberculosis, caseous pneumonia, caseous bronchitis, tuberculosis of the intestines, tuberculosis of cattle (murrain), and tuberculosis produced in animals by inoculation, to be identical diseases.

After the completion of these experiments, *Koch* still busied himself trying to solve two questions, viz.: Where the parasites originated, and how they gained entrance into the body. As regards the first question, he found that the bacilli multiplied only at temperatures between 30° and 41° C. Below 30° and above 42° C. not the least growth manifested itself in three weeks, time. He concluded from this that tubercle-bacilli, unlike the bacilli of splenic fever, can develop and multiply only in the animal body between certain limits of temperature. The

second question, he answered, by the conclusion that the majority of cases of tuberculosis have their beginning in the passages of respiration, the infecting matter generally manifesting itself at first in the lungs or the bronchial glands. It is, therefore, probable, he thinks, that tubercle-bacilli, clinging to particles of dust, are breathed in with the air at every inspiration. The bacilli are undoubtedly scattered throughout the air by the sputa of phthysical individuals. That this has stupendous evil results is evident, when it is remembered that one-third of all mankind are affected with phthisis.

Koch next instituted a series of experiments with the object of ascertaining the frequency of these bacilli in the sputa of phthysical individuals. He found that, in many cases, no bacilli were present; but in one-half of the cases examined they were found in large numbers. Bacilli were never found by him in sputa of non-phthysical individuals. He also inoculated animals successfully with sputum containing tubercle-bacilli. He found, furthermore, that dried sputa does not lose its virulence; he inoculated guinea-pigs successfully with dried sputa two and four weeks old.

Thus we owe credit to *Koch* for a great advance in medical science, if his experiments and results are to be relied upon; for to him belongs the merit of having established beyond dispute the fact of the para-

sitic nature of an infectious disease, the most important one affecting the human family.

Let us for a moment recapitulate and systematize his results :

1. Rod-shaped bacteria occur constantly in tuberculous organs of man, which are distinguished by peculiar chemical and morphological features from all other known micro-organisms. *Koch* names them "tubercle-bacilli," or the "bacillus tuberculosis."

2. Tubercle-bacilli are constantly present in tubercles, frequently in the sputum of tuberculous individuals.

3. Tubercle-bacilli may be cultivated from tuberculous substances, in a peculiar culture-fluid or nutritive stratum or soil.

4. Animals, inoculated with this pure culture-bacilli, become tuberculous.

5. In the nodules produced by inoculation, bacilli are also constantly found.

6. Bacilli may also be purified and cultivated from these inoculation nodules.

7. The bacilli thus cultivated are again inoculable.

8. Tubercle-bacilli grow and multiply only at temperatures corresponding to the temperatures of animal organisms. They are, therefore, true parasites.

9. All counter-experiments prove negative, and no development of tubercles follow.

10. Tubercle-bacilli are also found in cases of caseous pneumonia and bronchitis, *at times* in scrofulous

glands and fungoid joint affections, also in the pearl-nodules of the lungs of tuberculous cattle, and in the tuberculous organs of ~~monkeys and~~ chickens. Caseous pneumonia and bronchitis of man, tuberculosis (murrain) of cattle, and tuberculosis of monkeys, are, therefore, identical with tuberculosis of man.

11. Finally, tuberculosis is a specific, infectious disease, caused by a specific micro-organism—the bacillus tuberculosis—which constitutes in fact the true tubercle-virus.

It will be seen, from the foregoing, that *Klebs* and *Koch* both started out with similar ideas and aims; but how widely different are their results! Both sowed tuberculous matter on nutritive soil; both cultivated micro-organisms; and both positively asserted that inoculations with these, produced tuberculosis. The bacteria cultivated by *Klebs* are entirely different organisms from those of *Koch*. The monas tuberculosisum is globular, the bacillus tuberculosis rod-shaped; the monas tuberculosisum has motion of its own, the bacillus tuberculosis only molecular movement; the monas tuberculosisum multiplies in fluids, the bacillus tuberculosis does not. The question comes up as to which is right; both certainly can not be in entire conformity with the truth; one must be lacking in something. The masterly work of *Koch*, the skill and deliberation displayed, the scientific clearness of his methods and results, certainly seem satisfactory. His results, indeed, have been confirmed on

all sides. At first, only here and there among the great body of scientific men, an unsatisfied individual appeared. In the great enthusiasm of the moment, any skepticism in reference to the newly-discovered parasite was almost entirely ignored. But gradually criticisms became more frequent and louder, and *Koch's* results were pronounced as too far-reaching. But we will devote the next chapter to this interesting part of the history of tuberculosis.

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CHAPTER VII.

INVESTIGATIONS SINCE KOCH'S DISCOVERY.

The publication of *Koch's* experiments and results, threw new vigor into the discussion of the much-mooted question concerning the real nature of tuberculosis; it acted as a great stimulus for renewed researches in the hope of additional discoveries and also for the purpose of verifying *Koch's* results and conclusions. *Koch's* suggestion that the proof of the presence of bacilli might possibly be of value in a diagnostic as well as a therapeutical way, soon set the whole medical scientific world searching for bacilli, and studying their nature and relations more systematically from a clinical standpoint.

A great stimulus was given also to a renewed search for micro-organisms in other diseases supposed to be infectious. The methods of experimenting originated by *Koch*, have led within a short time to the discovery and announcement of a number of specific bacteria. *M. L. Bel*¹ found the bacillus of measles; *C. Burger*,² of Bonn, found a special bacillus in the sputum of

¹ The Lancet, London, March 3, 1883.

² Ibidem.

pertussis; *Dr. Sternberg*¹ the specific micro-organism of gonorrhœa; *Robert Morison*,² a peculiar form of bacteria in syphilis, and finally, *Crooke*³ described a bacillus found in the nasal discharge and in the sero-purulent exudation from the inflamed lymphatic tissue of the neck, in scarlet fever. Thus mycology was enriched in more than one way.

*Ehrlich*⁴ modified *Koch's* method of staining somewhat, and this later method has now almost replaced the original one. The tuberculous material (sputa) is crushed between two cover glasses; the cover glasses are then separated, dried and slightly heated over a Bunsen burner; they are then placed in an alkaline methyl-violet solution,⁵ where they remain one-quarter to one-half hour; they are next immersed in a mixture of officinal (Germ.*Pharm.) nitric acid and water (1:2) for a few seconds until they lose their color. Finally the preparation is colored brown by vesuvin, the bacilli appearing as violet-colored rods on a brown background. *Koch* supposed that the bacilli colored with an alkaline aniline dye, do not, when brought in an aqueous solution of vesuvin,

¹ Philadelphia Medical News, 1883.

² Wiener Med. Wochenschrift, No. 3, Januar 20, 1883.

³ The Lancet, London, March 3, 1883.

⁴ Deutsche Med. Wochenschrift, No. 19, 1882.

⁵ Water is shaken up with aniline-oil, filtered, and an alcoholic solution of methyl-violet added drop by drop, until it becomes opalescent.

give up their color as do the other tissue-constituents of the preparation. *Ehrlich* proceeded on the theory that the bacilli, colored with the alkaline aniline dye, do not lose their color in nitric acid. In the method of *Ehrlich*, in contradistinction from that of *Koch's*, the vesuvin is not regarded as a re-agent, but as serving only to give the preparation a brownish color which makes it much easier to find the bacilli.

*Heneage Gibbes*¹ introduced a further modification by using magenta aniline solution and chrysoidin, and claimed better results than those of *Koch* or *Ehrlich*.

Everywhere throughout the world, but, at first, especially in Europe, the medical profession now set to work to search for the bacilli of tuberculosis and every available case was examined. It would far exceed the limits of this volume to mention the results of all these investigations; but the great importance attributed to the presence of bacilli, their numbers, etc., warrants some notice of some of the more extended of these observations and the criticisms attending them.

*Ehrlich*² examined the sputa of twenty-six tuberculous individuals and demonstrated the presence of *Koch's* bacilli in every case. He also examined cases of other lung affections with negative results.

Fraenztel and *Balmer*³ observed the invariable

¹ The Lancet. London, Dec. 1882.

² L. c.

³ Berliner, Klin. Wochenschrift No. 45, 1882.

presence of bacilli in one hundred and twenty cases of tuberculosis.

All cases of lung affections entering the hospital at Heidelberg¹ in June, July, and August, 1882, were examined, and while bacilli were constantly found in cases of tuberculosis, they were in no case present in other lung troubles. This result has, probably, with very slight exception, been verified by hospital physicians generally.

*Lichtheim*² agreed in general with *Koch's* conclusions. He thought also, guided by results of his investigations, that the presence of bacilli in sputum is due to tuberculous destructive processes in the lungs, and that the destroyed parts always communicate with the air passages. *Lichtheim* found microorganisms in the excrements of both tuberculous and non-tuberculous individuals which reacted in the same way under *Ehrlich's* method as the tubercle-bacilli.

*Hiller*³ found bacilli in two out of three cases of hæmoptysis, in the blood expectorated. He furthermore inoculated two guinea-pigs with sputum containing bacilli from patients with hæmoptysis, and produced tuberculosis in both cases.

*Williams*⁴ found bacilli in two cases of hæmoptysis, in the blood expectorated

¹ Personal communication to author.

² Fortschritte der Medicin, Bd. I., 1883.

³ Deutsche Med. Wochenschrift, No. 47, 1882.

⁴ The Lancet, Feb. 24, 1883.

Chiari,¹ in a large number of examinations of sputa of phthisical persons, often found bacilli, and regards the occurrence of bacilli in sputa as a certain diagnostic sign.

*Craemer*² found rod-shaped bacteria in the faeces of perfectly healthy individuals which gave the same reaction with coloring fluids as the tubercle-bacilli.

*Formad*³ examined sputa of phthisical persons and in a certain number of cases failed to find bacilli. This and other observations mentioned, led *Formad* to oppose the view of *Koch* and the theory of specificity generally.

Lichtheim demonstrated the presence of tubercle-bacilli in the pelvis of the kidney in a dead body; and, very recently, *Prof. Rosenstein*,⁴ of Leyden, described a case in which bacilli were found in the urine in considerable numbers. He regarded their discovery of great importance diagnostically since the symptoms of uro-genital tuberculosis were otherwise equivocal.⁵ The bacillus has also been found, as

¹ Wiener Med., Presse, No. 1, 1883.

² Sitzungsbericht der Societät in Erlangen, Dec. 11, 1882.

³ Philadelphia Medical Times, Dec. 18, 1882.

⁴ Centralblatt f. die Med. Wissenschaften, 1883.

⁵ *Dr. Babes* also reported in the last number of the Progrès Med., March, 1883, three cases of tuberculosis of the uro-genital system, in which tubercle-bacilli were found. This is, in reality, the first publication made in France concerning the tubercle-bacillus discovered by *Koch*.

the records show, in an ulcer of the tongue, in lupus, and in an unopened knee-joint.

*Kowalski*¹ made extended observations with regard to the presence of bacilli in the sputa of persons with lung affections. His investigations extended over almost a year; during this time he examined six hundred cases and made some three thousand microscopical preparations. In not a single case of non-tuberculous affections did he find bacilli present, while in most cases of tubercular phthisis he found bacilli, sometimes at a stage of the disease when it was not possible either from the history or the physical signs to make a positive diagnosis. He regards, therefore, the detection of bacilli as a perfectly reliable and certain diagnostic sign. Twenty-two cases more carefully examined by him corroborated the statement of *Koch*, that the bacilli, at first present in small numbers, become more numerous as the disease progresses, and sometimes just before death are found in large numbers.

*Heron*² found the tubercle-bacillus in fifty-four cases of phthisis, and thinks that practically it may always be found in cases where the physical signs of phthisis existed. In some cases, even where otherwise he would have hesitated to make the diagnosis because the physical signs were so slight, he made it

¹ Wiener Medizinische Presse, Feb. 24, 1883.

² Proceedings of the Med. Society of London, Feb. 12, 1883. Lancet, Feb. 24, 1883.

on the presence of the bacillus. As regards prognosis, he thought a few bacilli betokened a chronic course; a large number and their persistent presence indicated a rapidly fatal course.

Dettweiler and *Meissen*¹ instituted a series of investigations in eighty-seven cases, in which the clinical diagnosis of phthisis, in various stages, had been made for the purpose of demonstrating the presence of bacilli and their relation to this disease. They also examined as to the presence of elastic fibers. They arrived at the following results.

1. In eighty-five out of the eighty-seven cases, bacilli were found in the sputa in larger or smaller numbers. In two, no bacilli, even after repeated examinations, could be discovered, although the patients presented well-marked physical signs. No elastic fibers were found in these two cases.

2. In eighty-two out of the eighty-seven cases, elastic fibers were demonstrated. They concluded, from these results, that where elastic fibers are found, bacilli are always present, and the greater the number of bacilli the greater the amount of elastic fibers.

3. The bacilli generally appeared in groups, in the interior of the cells, or isolated, outside of them. They were most numerous in cheesy particles that are present at times in the sputa. The number of

¹ Berliner Klin. Wochenschrift, Nos. 7 and 8. Feb. 12 and 19, 1883.

bacilli found bears no relation to the intensity of the disease.

4. They found, however, in very severe cases with high temperatures, profuse expectoration, and extensive destruction of tissue, bacilli always in large numbers. In cases of incipient phthisis the bacilli, on the contrary, were generally scarce. The height of the fever seems to exert some influence on the number of the bacilli. Thus, in the eighty-five cases where bacilli were found, fifty cases had no fever while thirty-five had. In the fifty cases, however, the bacilli were numerous in fourteen cases and scarce in thirty-six; while in the thirty-five cases with fever, eighteen showed bacilli in large numbers, seventeen in less numbers but still moderately numerous.

Detweiler and *Meissen* lay great stress upon the fact that destruction of lung-tissue and the presence of bacilli go hand in hand. They also oppose the contagiousness of phthisis.

Throughout Germany, soon after *Koch's* experiments, since the bacilli were found in all phthisical individuals, and since, by inoculation with these bacilli, tuberculosis could be produced experimentally, it was immediately concluded that the bacillus was the cause of tuberculosis, and, therefore, tuberculosis was a true infectious disease like syphilis, which could only be transmitted from person to person by direct contact. A peculiar something—a “disposition”—however, was necessary for the growth and development

of the bacilli. From a clinical standpoint *Dettweiler* and *Meissen* do not regard tuberculosis as contagious. It is difficult, they say, to overcome or circumvent the peculiar disposition—the still hypothetical nutritive soil—as also to harmonize the etiological, symptomatic, and pathological-anatomical features of the experimentally-produced inoculation-tuberculosis with chronic phthisis pulmonis. *Aufrecht*¹ also warns against coming to hasty conclusions, and claims that the tuberculosis produced in animals by inoculation with tuberculous materials, is entirely different from chronic phthisis. *Dettweiler* and *Meissen* conclude that phthisis is a disease *sui generis*, having many causes which lead to its production, and does not depend on infection. This latter assertion they base on the report of statistics of various hospitals, notably the Brompton Hospital,² where, during twenty years among the physicians, attendants, and nurses, who were healthy on entrance, not a single case of lung trouble has appeared, although they had handled fifteen thousand two hundred and sixty-two patients occupying the same building with them, most of whom were suffering from some form of phthisis. They furthermore concluded, that the bacilli were not the cause of tuberculosis, but supposed that the phthisical lung furnished a good nutritive soil for the development and multiplication of the parasites.

¹ Verein der Aerzte. Madgeburg, June 4, 1882.

² Lancet. London, June, 1878.

The bacillus does not cause, but simply accompanies and complicates tuberculosis

*Schottelius*¹ thinks, that the occurrence of tubercle-bacilli in the most varied diseased processes, both clinically and anatomically different from each other, makes it more probable that their active influence is only a conditionally pathogenic one. So far it has been proved only that under certain circumstances tuberculosis may be produced with tubercle-bacilli. It is not proved that one is able, with this virus alone, to call forth the pathological complex of symptoms called tuberculosis. If *one* tubercle-virus has been found, it should not be claimed that *the* tubercle-virus has been found.

*Gibbes*² has called attention to two points: First, the difference in the structure of miliary tubercles of the lungs and the relation of the bacilli to these different forms; and, second, the presence of bacilli in the smallest or commencing tubercles. The post-mortem appearance of these two forms of tubercles is similar. Microscopically, however, the tubercles of the one kind are of the reticular form, consisting of a distinctly fibrillated structure with one or more giant-cells and a caseous mass in the center; in the other form, the tubercles are non-reticular, having no fibrillation, no giant-cells, but consisting of irregu-

¹ Virchow's Archiv, Bd. 91. 1883.

² Lancet, London, Feb. 24, 1883.

lar cells in the periphery, and a caseous mass in the center. In the one form the surrounding vesicles contain catarrhal products, and, in the other, fibrinous exudation. A large number of lungs affected with the reticular form were examined by *Gibbes*, and bacilli found in only three cases, and in these in small numbers, distributed through the reticulum. In the non-reticular form, however, bacilli were invariably found in large numbers in the caseous center. He furthermore pointed out that the bacilli are present in the smallest tubercles; that often, moreover, the lung may be filled with tubercles, each one containing thousands of bacilli, and yet the patient die before the destructive process had gone far enough to cause any of them to be ejected with the sputa. Thus, there were two forms of fatal tuberculosis in which no bacilli could be found in the sputa. He adds that he examined the lungs of guinea-pigs that had become tuberculous after being kept in the air-shafts of the Brompton Hospital, and found no bacilli in them; he also mentions a case in which a guinea-pig, inoculated with sputum from a case of phthisis, presented a glandular abscess in the thigh, which abounded with bacilli, whereas the internal organs, although full of tubercles, did not yield a single bacillus.

*Williams*¹ examined the sputa of one hundred and

¹ The Lancet, London, Feb. 24, 1883.

thirty cases of lung affections in the Brompton Hospital. Every precaution possible was taken; if bacilli were not found on the first examination, the examinations were repeated again and again. Twenty-one cases were examples of various lung affections other than phthisis; two were cases of asthma, three of bronchitis, five of emphysema, two of bronchitis and emphysema, one of pleurisy, three of bronchiectasis, one of pneumonia, one of empyema, two of pulmonary congestion (the result of heart disease), and one an obscure case of lung induration. In not one of these did the sputum contain bacilli. The one hundred and nine phthisical cases consisted of acute and chronic forms, and included instances of tuberculo-pneumonic phthisis, of serofulous pneumonia, of fibroid catarrhal phthisis, and a large number of cases of chronic tubercular phthisis. Cavities were detected in one or both lungs in eighty-one of these patients; nine were in the stage of early consolidation; the rest were undergoing softening, or were cases of old tubercular induration with emphysema and fibrosis. Bacilli were detected in one hundred and six out of the one hundred and nine cases examined. He also states that the fact that no bacilli were found in the three cases of bronchiectasis, in which the expectoration was extremely fetid and abundant, separates the tubercle-bacillus from any of the numerous organ-

isms connected with fermentation and decomposition.¹

As regards the relation of the bacillus to the question of the contagion of phthisis, he also gives his views and results. It must be ascertained in the first place whether they exist in the air exhaled by consumptive patients as well as in their sputum. *Ransom* found them in the air of a room containing several advanced cases of phthisis, and *Smith* detected them in a respirator worn by a patient. *Williams* suspended glass plates covered with glycerine in the extracting flues of the Brompton Hospital, and subjected them to a stream of air with a velocity of three hundred to four hundred feet a minute, issuing from numerous wards containing consumptive patients. In this way he sought to obtain a concentration of the exhalations, and on testing the plates they were found to

¹I might mention in this connection a case that was communicated to me personally, and has not, as yet, found its way into print. A patient was admitted into one of the great medical wards of Vienna, and, as is customary in every case of lung trouble, was examined for the presence of bacilli. Physical examination showed most marked bronchiectasis present, but when it came to the examination for bacilli, it was found by three assistants, independently of each other, that bacilli were present in large numbers. Repeated examinations gave the same results. In view of these facts, the diagnosis tuberculosis was made. Post-mortem examination, however, showed that the physical examination was correct, most extensive bronchiectasis being found and not a sign of tuberculosis.

contain abundant bacilli. Taking into consideration the great amount of sputa, which, when dried, is disintegrated and inhaled in our streets, it must be admitted that if the **bacillus is the agent** of infection it is a very wide-spread one. How are we to account, therefore, for the comparatively few instances of infection? The evidence of the Brompton Hospital negatives any idea of its contagion, in the ordinary sense of the term, the number of cases of phthisis occurring among the resident staff being fewer than at some general hospitals even. Intimate association, also, with a consumptive person, such as the relations between husband and wife, mother and daughter, two sisters, and members of the same family living together, ought to insure certain contagion; but observation shows that this is not the result; some cases may be contracted in this way, but they are few in number. *Williams* offers the explanation that the bacillus requires, in every instance, a congenial soil to enable it to multiply and to carry on its work. Such soil, he says, is found in individuals who have been subjected to one or more of the well-known predisposing causes of consumption—such as heredity, bad food, bad ventilation, over-work of mind or body, unhealthy occupations, damp soil—which bring about that blood crisis, or weakness of constitution, which shows itself in various low inflammatory processes, in the exudation of leucocytes, in the formation of giant-cells, in adenoid hyperplasia, in the tendency

to form and exude cells which grow and do not develop into tissue, but die and caseate. The bacillus penetrating to the lungs of such subjects probably sets up centers of inflammation, giving rise to adenoid hyperplasia and the formation of miliary tubercles, and then spreading through the lymphatics, it assists in the work of consolidation and destruction. In the walls of the cavities it probably finds the best conditions for growth and development, viz: Warmth and moisture. People in good health, with sound organs, in full physiological activity, may defy these organisms, and it is probable do inhale them with impunity. While, therefore, *Williams* further remarks, the bacillus must be duly considered in the origin of phthisis, it may be regarded as only a more or less exciting cause of the disease, requiring a previous weakening of the constitution to enable it to act. It is, however, possible, if in great numbers and under specially favorable circumstances, such as are to be found in the South Pacific Islands, even that individuals not predisposed may be attacked, and that the disease may run a particularly short and virulent course.

Mention must also be made of the publications of *Benecke* and *Schmidt*.

*Benecke*¹ reports that he found in an alcoholic etherized extract from healthy blood, formations which

¹ Die erste Ueberwinterung auf Norderney, Norden. 1882.

presented the same appearances as *Koch's* bacilli and reacted in the same way. He thinks the bacilli discovered by *Koch* have no claim to the title of micro-organisms. www.libtool.com.cn

*Schmidt*¹ endeavors to prove that the bacilli of tuberculosis discovered by *Koch* represented merely the minute crystals of fatty acids, and therefore are not bacilli at all. Neither does he attach any significance whatever to the presence of bacilli or other minute organisms in the expectoration of tuberculous patients, because the germs of these organisms had, with each inspiration, ready access to the cavities of the lungs. It is a common occurrence, he says, to meet with micrococci, even in the sputa of non-tuberculous persons, and he thinks that the assertion of any minute organism being the cause of tuberculosis is invalid as long as this organism is not met with in the blood. As regards the bacilli which *Koch* raised from tuberculous matter, he always regarded with suspicion organisms obtained by culture from pathological tissues or secretions, for the obvious reason that their germs appear to be omnipresent and the experimenter hardly knew himself the origin of all the bacteria which he found in his culture-fluid.

It can not be doubted for a moment that both *Benecke* and *Schmidt* went much too far in disputing that the bacilli discovered by *Koch* are not micro-organisms; too many observers have found to the con-

¹Chicago Medical Journal and Examiner, Dec. 1882.

trary. The existence of the bacillus itself is a settled fact, and the great question of the nature of tuberculosis hinges on entirely different considerations.

This is an outline of the discussions, the investigations, and the criticisms, following the announcement of *Koch's* discovery, scattered as they were throughout the whole medical literature of the world. So far the tendency has been to confirm and corroborate his investigations and his great discovery stood almost unchallenged. Here and there faint opposition manifested itself in the various writings of the authors mentioned. It was only very recently that *Spina*,¹ assistant in Prof. Stricker's laboratory, announced a series of investigations which were calculated to overthrow *Koch's* theory which had already gained so firm a footing; and, since *Koch's* and *Spina's* results are almost diametrically opposite and represent the two extreme aspects of the discussion, I will devote the remainder of this chapter to a detailed abstract of *Spina's* experiments, results, and views.

The investigations of *Spina* extend over almost a year; he takes up separately every claim of *Koch's* and produces arguments and experiments to invalidate and disprove them.

He denies the statement of *Koch* that tubercle-bacilli react in a characteristic way with the aniline dyes. This was one of *Koch's* main points, for thus

¹ Studien ueber Tuberculose, Wien. 1883.

mycologists would be able to prove with the precision of a chemist the presence of tubercle-bacilli under the most varied circumstances. *Koch* and *Ehrlich* also thought that aqueous solutions of vesuvium and acids did not penetrate the interior of the bacilli, and that therefore they were clothed with a peculiar membrane which acted as a barrier. Until then no form or kind of cell had been known which possessed this peculiarity. *Spina*, from a series of experiments, disputes the statement of *Koch*, that the solution of aniline dyes must have an alkaline reaction, in order to color the so-called tubercle-bacilli. He found that not only alkaline, but neutral and even acid solutions of these coloring matters, color the bacilli in tuberculous lungs. He furthermore disputes the claim that acids do not enter the tubercle-bacilli. *Ehrlich*, as was seen, held that after the preparation supposed to contain bacilli had been stained with an alkaline methyl-violet solution, if it was now immersed in nitric acid, the coloring matter was eliminated from all parts of the tissue with the exception of the bacilli. The acid, therefore, *Ehrlich* concluded did not enter the bacilli. *Spina* watched microscopically the changes taking place when the acid was added to the preparation under the cover glass, and found that, the moment that the acid entered, a series of changes of color took place in the bacilli previously colored blue, they changing first into green, then yellow, etc. If a drop of water is now added, the same changes of color in an opposite direc-

tion take place. This experiment, *Spina* holds, proves conclusively that acids enter the bacilli. *Spina* disputes the assertion also that aqueous solutions of vesuvin do not gain entrance into the bacilli. He shows, as before, by microscopical examination, that vesuvin does color the tubercle-bacilli brown. Thus *Spina* concludes that the so-called tubercle-bacilli are not, at least so far as the reactions mentioned by *Koch* are concerned, cells of a distinct and peculiar kind, but are constructed like other cells of the animal and vegetable kingdoms.

Spina next attacked *Koch's* statement that bacteria, which stand in no causal relation to tuberculosis, react differently with coloring matter from the tubercle-bacilli. He shows, by a series of experiments with putrescent blood, decomposed serum, etc., that the bacteria occurring during decomposition react with coloring fluids as do the tubercle-bacilli. *Balogh*¹ had already made observations in accordance with this view and had found that certain bacteria present in stagnant marshy waters, gave the same reaction as the bacilli of *Koch*.

Before going on with an account of the observations and results of *Spina*, it will, perhaps, help to a better understanding of some of his subsequent results and views, to allude to two important hypotheses which different mycologists to-day hold on one and the same

¹ L. c.

subject. These relate to the constancy of micro-organisms—the question as to whether micro-organisms retain under all circumstances their original forms. As yet, this question has not been satisfactorily answered, mycologists being divided upon it into two classes diametrically opposite in their opinions. One hypothesis is, that the form of bacteria is variable, inconstant, depending upon the affinity which micro-organisms show to one or another of the nutritive strata with which they are brought into contact; and as the nutritive soil undergoes certain changes, so the micro-organisms living in it likewise change.

Naegeli and *Buchner*¹ are the principal champions of this theory. *Buchner* has shown by numerous experiments that hay bacteria undergo a series of visible changes, when slight changes are made in their nutritive material. *Naegeli*² also showed experimentally that certain “spalt-pilze” do not possess a constant form. He furthermore demonstrated that colored micro-organisms could be rendered colorless by cultivation and colorless organisms, colored.

The second hypothesis denies that any distinct kind of bacteria undergo changes, and ascribes to every species of micro-organisms a constant form and structure. This hypothesis has probably gained more ad-

¹ Untersuchungen ueber Niedere Pilze, page 205.

² Ibidem, page 129.

herents among physicians and especially clinicians than the first. Many experiments have been made to substantiate and support this hypothesis, but so far no experimenter has been able to contradict directly the results obtained by *Naegeli* in his experiments. *Koch* is an adherent of the latter hypothesis, and *Spina*, as will be seen, a warm friend of the former.

Spina undertook two series of experiments, making it his aim in the first series to test and analyze the claim of *Koch* that the dimensions of tubercle-bacilli varied only within certain well-defined limits, and that they were, therefore, special, distinct, and constant organisms. In the second series he endeavored to find bacteria which should possess the same dimensions as tubercle-bacilli, and should have no connection with tuberculosis.

1st Experiment.—Sputa from a woman. Clinical history: Had been sick for eighteen days; high fever, dullness in both subclavicular regions, with bronchial breathing. Death followed on the twenty-first day. Post-mortem showed acute miliary tuberculosis of the lungs, the pleurae, the liver, and the spleen. Sputa treated according to *Koch's* method. Next day very slightly stained (blue) bacilli were seen, also several short, thick rods (ratio thickness to length 1:2), colored as the rest of the bacilli.

2d Experiment. Sputa from a tuberculous woman. Treated according to *Ehrlich's* method. Numerous bacilli of slender shape, but in most cases as

long as they are thick. Among this number were numerous rods, half as long and once again as thick as the smallest of Koch's bacilli.

3rd Experiment. Sputa from a tuberculous man. Clinical history and physical signs well marked. Sputa stained according to Koch's method. Preparation contained several thick, short rods, colored blue. Length in proportion to the thickness as 3:1.

4th Experiment. Sputa from a tuberculous woman. Treated according to Koch's method. Several short, thick rods (1:3) and small granules are observed colored blue. Near the edge of the cover-glass several red blood-corpuscles have also been colored blue.

5th Experiment. Sections of a tuberculous lung that had been hardened in absolute alcohol. Sections treated according to Koch's method, and examined under glycerine. One section shows microscopically at the margin of the caseated metamorphic tubercle-tissue several blue-colored bacilli having the appearance of the Koch bacilli. The cheesy, degenerated tissue, which, according to *Aufrecht* and *Baumgarten* is composed almost entirely of bacteria, shows none of these. The same preparation is now washed for twenty-four hours in water and then treated according to *Ehrlich's* method, with nitric acid in the usual way. After this procedure, it is again examined microscopically, and shows numerous violet-colored rod-shaped bodies and granules in the cheesy parts of the tubercles. The rods are thicker and about

one-third smaller than the ones found near the margins. These latter now appear colored brown. The preparation is again treated with nitric acid, washed thoroughly and subjected to *Koch's* method a second time. The next day the microscope shows that the margins of the caseated parts again contain bacilli colored blue, while the caseated parts themselves are entirely free from them. These results show that blue-colored, rod-shaped bacteria occur in the most varied forms. If, however, the blue color can not be taken as a sure sign of the presence of *Koch's* bacillus, what special characteristic is it that marks the bacillus as a specific micro-organism? Not their dimensions, certainly. For how does *Koch* know that bodies of certain dimensions are tubercle-bacilli? When it is demonstrated that other forms of bacteria occur in tuberculous matter, it can not be said positively that only one of these forms is endowed with specific action. "What could *Koch* say, if I should consider the shorter and thicker bacilli as the specific ones?" So argued *Spina*.

Spina also made a second series of investigations in order to show that *Koch's* tubercle-bacilli also occur in non-tuberculous substances.

1st Experiment. Sputa from a man suffering with croupous pneumonia; a small bit of the tenacious, rust-colored sputum, is pressed between the slide and cover-glass and examined microscopically. Several short, thick (1:3), rod-shaped bacteria are observed.

The preparation is now transferred to the moist-chamber for three days, and then re-examined. Small, round granules are now seen, as also bacteria of the form and size of *Koch's* tubercle-bacilli. These show only "molecular" movement.

2d Experiment. Sputa from a man with bronchiectasis; microscopical examination shows, besides bacteria of a short, thick form, others identical with *Koch's* bacilli. No motion of their own.

3d Experiment. A thick thread is drawn through the muscles of the thigh of a rabbit. The animal is killed five days later. The thread is surrounded by thick pus. The post-mortem does not reveal any signs of tuberculosis. Several particles of the cheesy pus are transferred to the moist-chamber and examined, several days later, under the microscope. Besides the usual pus-cells, round granules, short, thick rods, and bacteria of the dimensions of *Koch's* bacilli, are found present. *Spina* therefore thinks that these investigations show that bacteria of different kinds found in tuberculous sputa, react in the same way with *Koch's* and *Ehrlich's* methods, and that on the other hand, bacteria of the same form as *Koch's* bacilli are present in diseased processes bearing no relation whatever to tuberculosis.

Koch's claim as to the constancy of the tubercle-bacilli was next tested by *Spina*. His results in this line were also unfavorable to *Koch's* assertions. He examined altogether eleven cases of chronic tuber-

culosis of the lung occurring in man, and one case in a monkey. He made some two thousand to three thousand sections through various lung tissues, and although a resumé shows that blue- or violet-colored bacteria occurred in a great number, these bacteria were found of various sizes, some short and thin, others short and thick, some long and slender, etc. His investigations also show, that in the contents of cavities, and in the vessels between the infiltrations of tubercles, colored bacilli are often present; but that, even when they are present, they are so small in number that a causal relation between them and the diseased process can not be taken for granted. The theory of an invasion of micro-organisms from without, gains strength from the fact that it seems more reasonable to suppose that we are dealing with organisms whose germs have gained entrance from without. Literature, too, contains various observations to this effect. Thus, *Baum*, *Litzman*, and *Eichstadt*,¹ found aspergilli in lung tissue; *Hasse* and *Welker*,² mucor in gangrene of the lung; *Leyden* and *Jaffe*,³ leptotrix in gangrene. In the lungs of diabetic subjects *Rosenstein*⁴ and *Slawjansky*⁵ found odium albi-

¹ Virchow's Archiv, Bd. IX.

² Küchenmeister Leipsig, 1855.

³ Deutsches Archiv für Klin. Medizin. Bd. II., 1867.

⁴ Berliner Klin. Wochenschrift, 1867. No. 1.

⁵ Jahresbericht von Virchow und Hirsch. 1867.

cans; *Cohnheim*¹ and *Heimer*,² *sacina*; *Furbinger*,³ *aspergilli*. *Friedländer*⁴ has observed micrococci in acute pneumonia. *Spina* examined tubercles found in parts of the body that do not communicate with the air, and especially those occurring in serous membranes. If the bacilli, he says, are the cause of tubercles they must be present constantly, without fail, in tubercles just developing. *Spina* examined one hundred and fifty mesenterial and omental tuberculous foci in various stages of development, according to *Koch's* and *Ehrlich's* methods, and was *not* able in a single instance to find bacilli. He experimented by transferring the serous membrane of man immediately after death to absolute alcohol, where it remained twenty hours, and was then immersed in a concentrated solution of methylene-violet for ten minutes. If the preparation appeared too deeply colored for microscopical examination, it was treated for a short time (one-third of a minute) with absolute alcohol until colored properly. It was then cleared with oil of cloves and mounted in Canada balsam. *Spina* was never able to find bacteria present. Only after the mesentery or omentum had been exposed to the air for twenty-four to twenty-eight hours did granules and rods appear, either scattered between the endothelium cells, or collected together in groups. *Spina*, also, cultivated

¹ Virchow's Archiv, Bd. 33.

² Deutsches Archiv für Klin. Med. Bd. 19.

³ Virchow's Archiv, Bd. 66. 1876.

⁴ Virchow's Archiv, Bd. 87. 1882.

omentum tubercles, in which his results were also negative and rather unfavorable to *Koch's* procedure of cultivation, which he criticises severely.

His results as regards the presence of tubercle-bacilli accord in almost all particulars with those of *Koch*. He found that in pronounced cases of tuberculosis *Koch's* bacilli may occur in great numbers, in small numbers, or they may be absent altogether. He calls attention, however, to these two points: First, that methylene-blue, as well as methylene-violet, be they ever so carefully prepared, at times give precipitates, which can be recognized as such only with good immersion lenses; second, that the solution of methylene-blue recommended by *Koch*—due to its alkalinity probably—acts, in regard to many bacteria at least, as a nutritive fluid, a culture substance. In warm weather great numbers of bacteria, partly colored and partly not, may be observed as early as three days after the preparation of the solution, which, nevertheless, remains perfectly clear. All these solutions should therefore be prepared fresh for each experiment.

Spina also examined the sputa of non-tuberculous individuals for bacilli, and in twenty-four cases of persons suffering from slight catarrhs of the pharynx and larynx he never met with *Koch's* bacilli. In the following cases his results were somewhat different and they are therefore detailed.

1st Case. I. W., twenty-six years old, had a slight pleuritis five years ago, as a result of which slight

dullness and retraction of the thorax, three fingers' breadth under the clavicle, are present. Since this time he has been in ~~excellent health, is~~ well nourished, and of strong, muscular development. Five preparations of sputa colored according to *Ehrlich* are made. All preparations contain *Koch's* bacilli. Three weeks later eight preparations are again made according to *Ehrlich's* method, and two of them contain together twenty bacilli of *Koch*.

2d Case. Person of rather phthisical habitus, thin and tall; perfectly healthy, however; thirty preparations of sputa, *Ehrlich's* method, contain numerous *Koch* bacilli.

3d Case. E. M., well-nourished individual, good, healthy complexion, and well-developed panniculus adiposus. Has had a catarrh of the larynx for five days; four preparations, *Ehrlich's* method, revealed no bacilli. Five days later eight more preparations were made, and short rods (1 : 3) found. Five days later eight preparations again made, three of which contained *Koch's* bacilli.

4th Case. H. C., a robust individual, tainted in no way. Eight preparations made, six contained small violet-colored granules resembling micrococci. One preparation contained four bacilli; the others were free from bacilli. A week after, no bacilli or micrococci were found in any preparations made; two weeks later, however, four preparations contained several *Koch* bacilli, also numerous violet-colored granules.

He, therefore, does not consider it sufficient to base a diagnosis simply upon the presence of a few bacilli, and thinks that the occurrence of bacilli in very large numbers alone might raise a suspicion of phthisis.

Spina finally criticises *Koch's* inoculation experiments. *Koch* inoculated with both tuberculous materials from man and tubercle-bacilli that had been cultivated and completely purified. In both series of experiments *Koch* developed nodules in various organs of the animals inoculated. That these nodules, however, represent tubercle-bacilli, says *Spina*, neither *Koch* nor his followers have proved. The history of the subject teaches that indifferent substances, coloring materials bacteria of decomposition, monas tuberculosum (*Klebs*), have all produced nodules similar to those produced by the tubercle-bacilli. *Spina* also made two inoculation experiments. In the first, he injected subcutaneously a speck of culture-bacilli into a rabbit, paying due attention to all antiseptic measures. The small wound healed by first intention. Eighty-six days after the injection the animal died. Post-mortem examination showed great emaciation, an abscess in the apex of the left lung, and a caseous nodule the size of a pea in the right, besides numerous smaller nodules scattered here and there. Nodules were present in the omentum and the peritoneum. The liver, the spleen, and the kidneys were normal. Microscopical examination revealed no entozoa in these nodules. In the second case, a rabbit was in-

oculated with the same material in the same way. Forty-three days after the inoculation it died. Thoracic organs normal, small whitish nodules in the peritoneum and the spleen; liver and kidneys normal. All nodules were found free from entozoa on microscopical examination.

An answer to *Spina's* criticisms soon appeared. In less than a month after *Spina's* publication *Koch*¹ himself responded, at the same time reviewing the various other criticisms, also, which his discovery and experiments had called forth since his first publication in March, 1882. During all this time he had been perfectly silent on the subject, seemingly considering the antagonistic views expressed as not worthy of notice and reply. Unfortunately, the later article of *Koch* contrasts unfavorably with the modest recital of his experiments one year before. He now fails to exhibit that cool, dispassionate, and characteristically scientific spirit which marked his first effort. He takes up the various views that have been expressed hostile to his discovery and instead of disproving them throws them all aside with the cutting remark, that all those persons who claimed to have found anything contrary to his results knew nothing of the use of the microscope, methods of staining, and mycology in general. But who is to judge what the standard shall

¹ Kritische Besprechung der gegen die Bedeutung der Tubercle-bacillen, Gerichteten Publicationen. Deutsche Med. Wochenschrift, No. 10, März, 1883.

be? Certainly the fact of not being able to find bacilli where *Koch* thinks they should be, should not characterize a man as an ignorant and a novice in microscopical examination.

Koch refers to the fact that every great discovery unexpectedly announced to the public at first meets with opposition and abuse. He calls attention to the history of the recurrens-spirochætes, which at first could not be found by many, but afterward became recognized by all. Speaking of the attention and interpretation which was given to his discovery in America, he characterizes it as perfectly ridiculous. He refers to the remarks of *Eph. Cutter*,¹ who said that *H. Saulesburg* had found in the blood, the lungs, and the sputa of phthisical persons, the mycoderma aceti, and that these were similar to *Koch's* bacilli, only smaller,—the “babies,” embryonic forms of bacilli tuberculosis. He next calls attention to a personal communication he had received from *Rollins Gregg*, who saw in phthisis but a loss of albumen in the blood, and claimed that, in every tubercle, fibrine filaments were present; he, however, had never made microscopical examinations, and, in fact, as *Koch* thought, knew nothing whatever of mycology. The investigations of *Schmidt*, *Formad*, *Lichtheim*, *Craemer*, etc., already mentioned in these pages, are next passed in review, and *Koch* concludes in a general way that all these observers were not masters of his staining and cul-

¹ American Med. Weekly.

ture methods, and he even doubts whether many of them would know the bacillus if they should see it.

Spina is vehemently and vigorously attacked—with words—and the same criticism is made upon him, namely, that he did not know how to work with the microscope, that he did not follow the methods of *Koch* carefully, in fact did not know how to microscope, cultivate, or inoculate bacteria. He closes by advising *Spina* to begin his experiments over again, after having mastered the manipulations necessary. The impartial reader can not but be unfavorably affected by this excited article of *Koch's*, which approaches closely his reply to *Pasteur*, whom he accuses of seeking notoriety, of not being master of his subject, etc.¹ *Koch's* article is certainly not sufficient to invalidate the statements of *Spina*.

Such have been the results of the most recent experiments on this great question; the one series overthrowing the conclusions of the other; the one assuming to have found the cause, the contagium of tuberculosis, the other holding that this supposition lacks any sufficient support and strength, and is not yet proved. Whether *Koch* has been too sanguine in the one direction, or *Spina* has gone too far in the other, it is not for us to decide. The great number of scientific men engaged throughout the civilized world in repeating these experiments, and in studying their re-

¹Zur Frage der Milzbrandimpfung. Eine Entgegnung zur Rede Pasteur's Gehalten in Genf. 1882. Von Robert Koch.

sults, will soon sift out the truth of the matter, and bring the question to a final and authoritative decision. www.libtool.com.cn

This much may, however, be said: We are yet on the threshold of a great discovery, and it will require constant inquiry, patient investigation, and deep research, before the true relation of bacilli to tubercles, and the part they play in their pathology and causation, are fully determined.

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