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ORIGINAL ARTICLES.

TRACHOMA.

ORIGINAL INVESTIGATIONS ON ITS ETIOLOGIC ORGANISM.

I. THE ORGANISM AS SEEN IN THE TISSUES AND SECRETIONS. II. AS SEEN IN THE CULTURES, III. SUCCESSFUL INOCULATION. IV. TOXINS AND ANTITOXINS.

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Statistics: showing the frequency, gravity and long continuance of trachoma.—Of 324 new patients received as house cases at the Illinois Eye and Ear Infirmary from June 1, 1898, to Nov. 1, 1898, 123, or about 38 per cent. were cases of trachoma. Other patients come and go, but trachoma patients stay on interminably, so that of 41 patients now under my observation, 23, or 56 per cent., are cases of trachoma. Trachoma can never be called cured. The lids may become perfectly smooth, and the disease seem apparently mastered, but in the course of a few weeks or months the patient will return with a trachoma which has all the characteristics of an acute disease.

Of 50 cases of trachoma, in which I made careful records, 38 were cases where the disease had endured over two years, 13 where the disease had lasted more than five years, 7 where it had lasted more than ten years, and in one case it had lasted thirty-eight years. Of the 38 cases which had lasted more than two years, there were only four which had had no corneal involvement; of these, one was employed about the hospital, and consequently had been under constant medical care, while in another case it was very doubtful whether the disease was trachoma or not. In no case where the cornea has once become involved, either through ulceration or pannus, does the patient regain normal acuity of vision. In my series of 50 cases the average acuity of vision was $2/7$, though this does not allow for refractive errors.

Between the dates of June 1, 1898, and Nov. 1, 1898, 122 patients were operated upon at the Infirmary; of these operations 41, or 34 per cent., were necessitated by trachoma. The figures do not include scarifications.

A patient who has once had trachoma is more or less unfitted for the active duties of life. Exposure to dust, heat, or bright light, residence in a malarial district, unhygienic surroundings, negligence in the use of the proper medicines, may bring on an acute exacerbation of the disease at any moment. In view of such facts as these, and with the present facilities for research at our command, when also we consider the vast amount of material which our dispensaries and eye clinics furnish, it strikes one as almost incongruous that the disease is so little understood, and our methods of attacking it, in consequence, so empiric.

Literature of trachoma.—Since the days when bacteriology became a science, trachoma has been regarded

as a bacteriologic disease. Any one watching the phases of the disease, its acute onset, its localization in isolated follicles, which seem to act as centers or foci of the disease, the softening and degeneration of these follicles, the development of cicatricial tissue, which seems to act as a bar to its further progress, the gradual decline, the recurring exacerbations, recognizes that all these point strongly to some insidious micro-organism at work in the tissues, which it is possible to control a while, but which, when a favorable opportunity presents itself, acquires new life and activity. Sattler¹ was the first who investigated the micro-organism of trachoma, and announced his discoveries at the Thirteenth Assembly of the Ophthalmological Society, at Heidelberg. In examining the secretions at different stages of the disease, he found a micrococcus which resembled the gonococcus. The cocci were of biscuit shape, joined in pairs, but separated from each other by an intervening space. They were most frequently seen in groups of two, three and four, at times in clumps. In stains and sections, they could be seen as dark dots. He employed liquid culture-media in the beginning, later solid ones, mainly blood serum, in which the trachoma cocci grew well, but not invariably. At the point of inoculation he was able in seven or eight days to discover pale yellow spots, which developed slowly. On microscopic examination, the organisms in the culture were found to be identical with those of the secretion. The inoculation of animals was negative, but one on the human conjunctiva produced the disease.

If the Egyptian disease and trachoma are identical, we must consider the work done by Koch² in Egypt. He judged two etiologic factors to be at work: one a diplococcus, identical with gonococcus, causing a grave type of the disease; another, a tiny bacillus which caused a less severe type of the trouble. Da Gama Pinto³ was unable to find micro-organisms in sections of the diseased conjunctiva, and in consequence doubted the correctness of the findings of the preceding investigators.

Michel⁴ studied the disease during an epidemic at the Aschaffenburg Waisenhaus, where there were 97 boys; of those who contracted the trouble, 55 had a mild type of the disease, 14 a grave one. He studied the conjunctival sections in 30 cases, with negative results, but subsequently, in studying some of these cases from the Aschaffenburg Waisenhaus at the Wurzburger clinic, he found a few cocci in the secretions.

In making sections of conjunctival tissue, Michel found cocci in the follicular contents, never in the epithelium. The work proved very difficult, on account of the minute size of the micro-organisms, and also on account of their scarcity. For the most part, he found them in irregular clumps; at times in rows of ten or twenty. He never found them within cells, but above or between them.

For his cultures, Michel used both conjunctival secretion and the contents of the trachoma nodules, which he either expressed or cut out. Cultures were only made in seven cases, and developed best from the expressed contents of the nodule. In several cases there was no growth. In one case the culture was contaminated by *staphylococcus pyogenes aureus*. In the successful inoculations on agar there developed after two days an even grayish-white thread-forming growth. On gelatin, at room temperature, there developed a grayish-white, thick layer, which grew rapidly on the surface, but along the stab and at its lower end developed small globules. At the end of four or five weeks a funnel-shaped growth had developed. The gelatin was not liquefied. On blood serum there appeared at the end of twenty-four hours a pale, even streak, which assumed a milk-like hue; at its periphery club-like prolongations appeared, which later assumed a ragged appearance. The pure cultures consisted of small diplococci, which resembled gonococci, but were smaller; their length from one pole to another was .6 to .8 μ ; width .4 to .6 μ . Inoculations on animals were negative, but an inoculation of the human conjunctiva caused the disease.

Schmidt⁵ found in the secretions small, round, isolated cocci, surrounded by a clear gelatinous area, and resembling *staphylococcus pyogenes aureus*. In the sections he found different forms. By staining sections according to Gram's method he found in the tissues round, point-like cocci. For cultures he used the secretion, and in forty-nine cases found a coccus resembling *staphylococcus pyogenes aureus*, though differing from it in size, motility and action toward gelatin. He claims to have caused the disease in birds.

Kukharski⁶ investigated twenty-six cases of trachoma and found numerous bacteria, among which were *staphylococcus pyogenes*, *bacillus subtilis* and *bacillus mesentericus vulgatus*. When these accidental organisms were excluded, his cultures showed one characteristic organism, of the size and shape of the gonococcus and possessed of a springing motion. He arrived at the following conclusions:

1. The etiologic factor of the disease is a bacillus which in some way becomes a coccus.
2. Michel's organism, which resembles a gonococcus, presents no characteristic feature.
3. The organism, in growing on solids, presents a white thread-like membrane consisting of confluent spots.
4. It liquefies gelatin; on the surface a white thread-like membrane forms.
5. The culture may be confused with *staphylococcus pyogenes albus* and other micro-organisms occurring in the air.
6. Inoculations from culture produced no effect.
7. Inoculation in the eye of a cat with the trachoma nodule itself caused the disease.

Goldschmidt's⁷ findings coincide with those of Michel. Washejewski⁸ studied thirty cases of trachoma in different stages. He found single cocci and groups of cocci in the lymphoid cells, red-blood corpuscles and epithelial cells. The cocci resembled gonococci. Baumgarten⁹ could not see that the specific organism of trachoma differed in any respect from *staphylococcus pyogenes aureus*. Staderini¹⁰ found similar cocci, as also did Schmidt-Rimpler. Wiltrams¹¹ results were for the most part negative. He found various cocci and bacilli, and decided that

thus far no one had proven anything definite. His conclusions were:

1. Various organisms are found.
2. In follicles are micrococci which are seen with difficulty.
3. Different authors describe different cultures, whose pathogenic characteristics at best are doubtful.
4. Most observers employed contaminated secretions.
5. The follicle itself should have been employed.

Schongolowicz¹² paid special attention to staining the organisms within the tissues. He used the Gram-Weigert and also the Koch methods, and succeeded in staining the organisms by both means. He found within the tissues bacilli 1 to 2 μ long, .3 to .5 μ wide. His cultures in three or four days disclosed on the surface of the culture-media round and oval colonies of granular structure. His bacillus displayed fairly rapid motion. It grew slowly on serum and rapidly on agar. Inoculations under the skin of two white mice, one guinea-pig and one rabbit gave no result. Inoculations of pure cultures on the conjunctiva of various animals produced not trachoma, but a somewhat similar disease. Alt¹³ finds round or oval cells containing one, two, three and four eccentrically situated round bodies which look like nucleoli. He thinks that in these bodies we have the organism causing trachoma. He was unable to find the organisms described by Sattler or Koch. Elze,¹⁴ observing that trachoma and malaria seem to thrive under similar conditions, and also observing some amelioration of the disease where quinin was given, judged that similar causes bring about the two conditions. He claims to have found in the secretions and nodules certain peculiar organisms which he judged to be monads and which he called "plasmodia."

As can readily be seen, the literature on this subject affords small help to one desiring to investigate the subject for himself, and still, in one respect there seems to be some unanimity of opinion, i. e., in regard to the presence of micro-organisms within the trachoma nodule. This side of the question also appeals to one from a clinical standpoint. What are these enlarged trachoma nodules? Simply enlarged lymphatics of the conjunctiva. Why are they enlarged? For the same reason, in all probability, that any lymphatic gland enlarges: they are filtering from the deeper tissues such noxious agents as are producing the disturbance, and if these agents are bacteria of any kind, here, in all probability, they are to be found. I therefore decided to start my investigations with the trachoma nodule itself, to subject it to the various methods of staining bacteria within tissues and see whether or not the micro-organisms could be found within that nodule. I employed the two well-known methods for staining bacteria in tissue: 1, staining with Loeffler's methylene-blue and decolorizing with acetic acid, 1 to 1000; 2, the Gram-Weigert method. Inasmuch as I slightly modified this latter method, it may be well to give briefly the different steps of the process: After anesthetizing the conjunctiva with a 4 per cent. cocain solution, the nodule is grasped with a small mouse-toothed forceps and snipped off with a sharp-pointed pair of scissors. Then it is: 1, placed in absolute alcohol six hours; 2, in xylol six to twelve hours; 3, infiltrated in paraffin; 4, imbedded in paraffin; 5, the section is cut. (The section must be very thin. I should call a section thicker than 1/150 millimeter worthless.) It is then placed: 6, in xylol; 7,

in alcohol; 8, in distilled water; 9, in Orth's lithium carmine twenty-four hours. (The lithium carmine must be well ripened; one must also remember not to fasten the section to the cover-glass with albumin fixative, as the lithium carmine does not stain well where albumin has been used.) Then it is: 10, washed in distilled water; 11, in anilin gentian violet fifteen minutes. (The anilin gentian violet should be freshly made each time. This is conveniently done as follows: a saturated alcoholic solution of gentian violet is kept on hand; in another bottle is kept a 5 per cent. solution of anilin water. Into a small dish 5 drops of anilin water are filtered through filter paper and into this 1 drop of gentian violet is dropped.) Finally, it is: 12, washed in normal salt solution; 13, dried and placed in Lugol's solution one minute; 14, in distilled water; 15, dried and decolorized with anilin oil till all violet color disappears and section looks red; 16, in xylol; 17, in Canada balsam.

When the Loeffler blue stain is used, tissues should appear perfectly colorless, while the bacteria stand out well stained. When the Gram-Weigert method is used, Orth's lithium carmine being employed as a counterstain, a beautiful picture presents itself when the section is placed under the microscope; the tissues are colored a brilliant red, in which the organisms are seen stained a deep violet.

In all, I prepared fifteen different sections according to these two methods. In every case I found within the nodule, organisms which presented striking morphologic characteristics. These organisms were present in greatest numbers in the loose adenoid tissue of the mucous membrane. They were commonly seen in small groups, usually in the intercellular spaces, though I have observed them in the leucocytes, in the protoplasm of the epithelial cells, and at times, in the blood-vessels of the nodule. The organism had a capsule, that I could say with certainty, but whether it was a capsulated diplococcus or a tiny capsulated bacillus with heavily staining ends I was not able to state with any degree of certainty, nor were a number of other observers. Its size could be accurately determined. It varied from 1.5 to 2 μ . in length, from .5 to .6 μ . in width. The organism was not decolorized by the Gram method of staining. I call special attention to this fact. When we remember that, with but very few exceptions, such as gonococcus, typhoid bacillus and a very few others, no pathogenic organisms are decolorized by Gram's method, while practically all non-pathogenic organisms are decolorized, the fact that this organism within the tissues was not decolorized seemed to me of great importance. In the meantime, I had prepared and examined according to the same methods four sections of hypertrophied conjunctiva taken from the upper cul-de-sac; in none of these sections could I find micro-organisms. This seemed to me to indicate quite clearly that the organisms were localized in the nodule.

I next tried to stain the organisms with carbol fuchsin, decolorizing with 10 per cent. sulphuric acid, but when this method was used no bacteria could be found. In three cases I slightly modified my *modus operandi*. Instead of cutting out the nodule and treating it as a tissue to be fixed, hardened, infiltrated and cut, I squeezed out the contents of the nodules, smeared them on a cover-glass, fixed them in the flame and treated them as smear preparations. In this manner one can study the micro-organisms to very

good advantage, and often obtain a far better definition than it is possible to obtain when the organisms are within the tissue. My findings in these last three cases corresponded with those previously described.

I now made a study of the secretions in thirteen cases. My results in these cases were rather unsatisfactory; in nine cases I failed to find the characteristic organism at all. In two cases I found it, but only in scanty numbers and after long search; in two cases it was found easily. One of these cases was one which I had myself inoculated, the other was a recent case, in neither of these two had astringents or antiseptics been used on the conjunctiva. In most of these thirteen cases adventitious organisms were present; not in the quantity one would expect where diseased tissue is exposed to the air, although in one case I found four distinct varieties of micro-organisms present. It is of interest to note that in four cases cocci were found which were decolorized by the Gram method of staining. In one respect the study of the secretions proved of great benefit, for I was now able to decide definitely and with positiveness as to the morphology of the organism.

The bacteria seen in the tissues, in the smear, and now in the secretions, were tiny, round, capsulated diplococci; at times it was still almost impossible to decide whether a particular organism was a very small bacillus with heavily staining ends or a tiny diplococcus, but in some preparations and especially those stained by the Gram method, it was possible to decide beyond the peradventure of a doubt as to the morphology of the organism with which we had to deal. These diplococci were surrounded by a clear, gelatinous capsule, which at times was remarkably clear and well-marked, at times almost impossible to perceive; the individual cocci were separated by a septum of the same kind, the septum, however, seemed often to have an affinity for anilin stains, especially Loeffler or Klebs methylene blue, while the capsule did not; the capsule could be especially well seen where the diplococci were turned on end, so that only one coccus could be seen surrounded by its gelatinous envelope. In many respects this organism was a miniature pneumococcus. It was of course much smaller than the pneumococcus and there was no lance shape present,

the elongation, if any, being in the opposite axis to that of the pneumococcus; still we must remember that pneumococci, and especially the younger forms, are very frequently round and not lance-shaped.

It may now be well to briefly review and tabulate the results of my studies of sections, smears, and secretions.

1. I found within the trachoma nodule in fifteen cases an organism varying in length from 1.5 to 2 μ ., and in width from .5 to .6 μ .

2. This organism was enveloped in a gelatinous capsule.

3. No other organism could be found within the tissues.

4. This organism was stained by the Gram method.

5. While seen only within the tissues or in smears, it was impossible to positively say whether this organism was a diplococcus or a small bacillus.

6. The organism was usually found in the adenoid

Growth on agar.

Growth on serum.

layer of the conjunctiva, most frequently between cells, though at times within them, very rarely in vessels.

7. It is quite abundant in the secretion of recent cases where no astringents or antiseptics have been used, but it is almost impossible to find after these have been used some time.

8. In the secretions it was possible to decide that the organism was a dot-like, capsulated diplococcus.

Agar culture, three days. Showing form of staphylococcus (without capsule). Stained by Gram's method.

The next task was to get a pure culture of the organism. This, with the data already in my possession, would, I thought, be a comparatively easy affair. It was a capsulated diplococcus, staining by Gram; these three facts alone almost isolated the organism. For my cultures I determined to again rely on the nodule. The conjunctival sac was well irrigated with a saturated solution of boric acid and then anesthetized with a sterilized 4 per cent. cocain solution. A small mouse-toothed forceps and sharp-pointed pair of scissors were next carefully sterilized, as was also a platinum loop. The lid was everted by an assistant, the nodule grasped with the forceps and snipped off; it was then crushed between the teeth of the forceps, laid on the platinum loop, and placed on the culture medium. By observing these precautions I was very successful in obtaining pure cultures, these being contaminated in only two cases.

My first inoculations were made on agar—2 per cent. glycerin agar and dog's serum. Of the first seven tubes inoculated, I obtained cultures in only two cases; one was a large bacillus decolorized by Gram's method, and the other consisted of clusters of cocci, stained by Gram's method. As was natural, when I saw the grape-like clusters of cocci not decolorized by Gram's method, I immediately thought I had to deal with some form of staphylococcus, which had in some manner gotten into the culture-tube. Somewhat disappointed at my lack of success with solid culture media, observing the same precautions as before, I inoculated seven tubes containing bouillon, taking the precaution of having the tubes warm at the time of inoculation and immediately placing them in the incubator. At the end of forty-eight hours two of these bouillon tubes were turbid and five remained clear. On making cover-glass preparations from the two tur-

DIAGRAMATIC

Bouillon culture, three days. Stained by Gram.

Secretion from case inoculated with trachoma. 1. Polynuclear leucocyte. 2. Transitional leucocyte. 3. Transitional leucocyte with diplococcus in cell protoplasm. 4. Epithelial cell with diplococcus in cell protoplasm.

bid tubes I found that in one was contained a mixed culture consisting of staphylococci and a tiny diplococcus surrounded by a clear, gelatinous envelope, which seemed in every way identical with the organism observed within the tissues and in the secretions; in the other tube I found a pure culture of this same diplococcus. From this pure culture, observing the greatest precautions so as not to contaminate my cultures, I inoculated one tube of agar, one of glycerin agar, one of dog's serum and one of gelatin. All these, with the exception of the gelatin tube, I placed in the incubator, and at the end of forty-eight hours found growths in all of them. I first made a cover-glass preparation from the growth on agar, and on placing it under the microscope was chagrined to find an organism which seemed to differ in no wise from an ordinary staphylococcus. Evidently I had contaminated my culture in changing from the bouillon

to the agar. I next examined the growth on serum; at the first glance this, too, seemed staphylococcus, yet on closer examination many of the cocci seemed to form pairs and some seemed to have a capsule. A cover-glass preparation was then made from the bouillon tube which had been inoculated from the original bouillon culture. It contained diplococci, although they seemed a trifle larger than the diplococci observed in the tissues and in the first bouillon culture, and the capsule also seemed less well marked. In some places they showed a tendency to form small bunches or clusters, in others to form chains of three or four, although these clusters or chains were always seen to be made up of diplococci. I now began to doubt whether the growths which I had observed on the agar and serum were after all ordinary staphylococci, especially as the macroscopic appearance of these growths was highly characteristic and differed from that of any ordinary staphylococcus; so I again inoculated bouillon tubes from these agar and serum tubes and the new growths in bouillon showed all the characteristic features of the mother bouillon culture, with the exception perhaps that the cocci seemed to have grown larger, and the capsule to have almost disappeared. Here then was a discovery, and one which explained the mistakes of many preceding investigators. The organism was modified in size and form by the character of the culture media; on solid culture media it simulated an ordinary staphylococcus, in bouillon it retained its characteristic morphology, and in the mother culture was of about the same size as when observed in the tissues, and had its capsule well marked, but on reinoculation in bouillon it became larger and lost its capsule. It was possible, however, even on the solid culture media, on careful observation, to observe that though the cocci were bunched like staphylococci, still these bunches were composed, not of groups of isolated cocci, but of bunches of diplococci. Whether this agglutination on solid media was due to the adherence of diplococci with each other or simply an agglutination caused by the medium itself I can not say.

I now inoculated a bouillon tube from the growth which I had obtained, we remember, on agar, in my first series of inoculations, and which I had judged to be staphylococci. The same thing again occurred; on making a cover-glass preparation I found only diplococci, some of them capsulated. My gelatin, in the meantime, had become very slowly liquefied on the surface by my growth, and here the organism was seen in an intermediate form, in some places showing the appearance of staphylococci, in others of diplococci. I now inoculated another series of ten bouillon tubes with trachoma nodules and in two more cases obtained pure cultures of the original tiny diplococcus.

I was now ready to inoculate animals. My first experiments were tried on a rabbit, a guinea-pig and a dove. The method employed was the following: Wrapping a small cotton swab tightly around the end of a probe, and placing some of the pure culture on the cotton, I massaged the conjunctiva till the cotton was tinged red. After the reaction caused by this massage had subsided there was nothing in the condition of any of these animals to indicate in the slightest degree that my inoculation was successful. At the end of two weeks any impartial observer would have pronounced the conjunctiva in the three cases normal. I next tried a rabbit which had been previously used for operative purposes and in each of whose eyes a

conjunctivitis existed at the time of inoculation. Here, at the end of a few weeks, I got a condition which somewhat resembled trachoma, but I must confess it had but little the appearance of a frank, acute trachoma, such as one sees on the human conjunctiva. It is true there were, and still are, isolated, enlarged, somewhat gelatinous-looking follicles, with some conjunctivitis, but there is none of that diffuse purplish hue, that velvety thickening of the mucous membrane, abundant secretion, roughening of the lids with enlarged follicles studding the palpebral conjunctiva, especially at the transitional fold, that one sees in an acute trachoma. I remember that, about a year ago, in experimenting on the conjunctiva of a rabbit, with a pure culture of streptococcus, I produced a conjunctivitis which in many respects resembled a trachomatous one. When we remember that one of the chief symptoms of trachoma is a miliary lymphadenitis due to the involvement of many tiny lymph-glands scattered about in the conjunctiva, it seems a very natural thing that any organism which will cause an involvement of these minute glands will simulate one of the chief symptoms of trachoma, although the disease may not be trachoma at all. In view of these facts, and also in view of the fact that I was unable to obtain the characteristic organism again in culture from these nodules on the rabbit's conjunctiva, I shall call my experiments on animals negative, although I still have this rabbit under observation and shall make other attempts to find the diplococcus in the nodules.

It was now my good fortune to obtain a human subject. An old woman, aged 68, blind in both eyes as the result of an explosion, and with a phthisis bulbi of the left eye, on being told that the experiment could in no wise injure her general health or condition, was induced, by the payment of a sum of money, to allow herself to be inoculated with the pure culture. I employed for this purpose a growth on agar, which had been inoculated from a mother culture of bouillon. At first I merely placed the germs in the conjunctival sac with a platinum needle. At the end of one week no reaction whatever had followed. I next employed the same method that I had used with animals. After cocaineizing the conjunctiva, I rubbed in the organisms till the cotton was slightly tinged. This time I was successful. For the first week the condition was one of simple conjunctivitis; there was redness, hypersecretion and a slight burning sensation. At the end of one week the picture changed slightly and the condition was rather that of a follicular conjunctivitis; the conjunctiva of both lids was of a deep red, the secretion had become more abundant, and on inspecting the mucous membrane with a convex lens, tiny, isolated, enlarged follicles began to appear. At the end of the second week the conjunctiva had become a deep, purplish red, was slightly hypertrophied and the enlarged follicles especially at the lower and inner border of the tarsal cartilage, had become more marked, and bunches of tiny vessels could be seen running to some of them. The case now presented that doubtful aspect which so frequently puzzles the oculist to tell whether the case is one of trachoma or merely a follicular affair. On the thirteenth day I found in the secretions a very small diplococcus, surrounded by a gelatinous capsule and stained by the Gram method; this organism was identical with the organism seen in the tissues and on the culture media. On the nineteenth day I inocu-

lated several bouillon tubes with the secretion and obtained this organism in a mixed culture. At the end of the third week, while the picture was by no means absolutely characteristic of trachoma, still if the patient had applied for admittance into the Eye and Ear Infirmary I should without hesitation have isolated her in the trachoma ward. At the end of four weeks I squeezed out one of the small follicles, smeared the contents on a cover-glass and found the organism in the smear. At the end of five weeks the diagnosis of trachoma could be made by the most impartial observer beyond a doubt. At the end of six weeks the appearance had become so characteristic, and there were so many of the diplococci present in the discharge, that fearing for the safety of the other members of the household, I began to treat the lids with strong solutions of silver.

I had now found the organism in the tissues and secretions, had obtained it in pure cultures on various culture media, had produced the disease on the human conjunctiva and once more recovered the organism. I will now for the sake of accuracy briefly tabulate and recapitulate all my findings in regard to this organism:

Origin.—Unknown; seems to occur most frequently in malarial districts.

Form.—Round diplococci, which in the tissues and first bouillon culture are enveloped in a gelatinous capsule. In the tissues they lie in small groups, each organism separate from the others. In bouillon they usually are seen as isolated diplococci, at times they are seen in small clusters or short chains, though the clusters and chains are always composed of diplococci. Often the diplococcus is seen turned on end, so that only a single coccus appears; in this position it is possible to see the capsule especially well marked. On solid culture media they simulate staphylococci, on gelatin they show an intermediate form.

Motility.—In the hanging drop the organisms exhibit a slight degree of motility.

Vitality.—Cultures die in bouillon in about two weeks; on agar they live for months.

Anilin stains.—Organism stains well with ordinary anilin stains; also by Gram method. Capsule does not stain, but septum between cocci seems at times to have an affinity for stains, especially for methylene blue, causing the organism often to resemble a bacillus.

Growth.—Grows rapidly in incubator, more slowly at room temperature. Bouillon becomes turbid in thirty-six hours. Abundant growth on serum in forty-eight hours. Grows somewhat slowly on agar, especially at room temperature. *On serum*: White, moist, membranous-like streak with a scalloped edge along line of inoculation. Edge is white, the center yellowish. *On agar*: Resembles somewhat the growth on serum; the edge exhibits the same scalloping. The growth on agar is more raised than that on serum. The difference in color between the center and the borders of the growth is even more marked; the center is distinctly yellow, while the borders are milk white. *In bouillon*: At the end of ten days, white, sand-like deposit settles at bottom of tube. *In gelatin*: Growth somewhat funnel-shaped. White, wavy, thread-like growth along the stab, consisting of small, agglutinated globules. Grows somewhat heavier toward the surface, and on the surface forms a white membranous growth which shows the same peculiar scalloping of the edges, as the growth on serum. The gelatin liquefies very slowly on the surface, but not along the stab.

Oxygen requirements.—Facultative aerobic.

Odor.—After developing one week, on any of the culture media, and especially in bouillon culture, it has a pronounced urinous odor, which, as time goes on, becomes very offensive.

We have now described a capsulated diplococcus not decolorized by the Gram method. It immediately becomes necessary to differentiate it from the only other diplococcus to which this description could apply, i. e., the pneumococcus. This is easily done. The trachoma diplococcus is smaller, has a slight degree of motility, a characteristic appearance on culture media which differs most decidedly from pneumococcus, and a very different pathogenesis.

I shall now compare my findings with those of other men who have investigated this subject, and especially of those whose results have in any measure coincided with my own.

Sattler, we remember, found biscuit-shaped cocci, which he compared to gonococci. Morphologically there is at times a great resemblance between the two organisms, but here all resemblance ceases, and the comparison for this reason was an unfortunate one. Morphology in bacteriology is a notoriously uncertain thing. A capsulated, dot-like diplococcus, staining by Gram's method, has very little real resemblance to gonococcus. Sattler relied too much on secretions. I found them far more apt to contain adventitious organisms than the one in question. Kukharski's criticism of Michel's work, when he says that Michel's organism presents no characteristic feature, applies even more justly to Sattler. Sattler failed entirely to characterize and individualize the organism he saw. He did not identify it, so that it must needs be the trachoma organism and nothing else.

Koch thought the disease a mixed infection. It is easy to understand how this came about; in all probability he saw the trachoma diplococcus. He saw it when it could not be differentiated from a tiny bacillus; again, he saw it when the diplococcus form could be plainly perceived, and consequently judged the disease a mixed infection.

Michel undoubtedly saw the trachoma diplococcus; from his descriptions of it, we can not doubt that fact, but Kukharski's criticism is just and well founded when he says Michel failed to characterize this organism; he also failed to describe the change of morphology on different culture media, a fact easily explained when we remember that he only inoculated seven tubes in all, and in a number of these tubes did not obtain growths.

Schmidt first mentions the capsule. He describes an organism resembling staphylococcus pyogenes aureus, which is surrounded by a clear, gelatinous area. In all likelihood he noticed the yellowish color of the organism on solid culture media; on examining it, found a staphylococcus form, and naturally judged the organism to be the staphylococcus pyogenes aureus.

Baumgarten also describes it as a staphylococcus, having in all probability seen the same form as Schmidt.

Kukharski found a bacillus which somehow became a coccus. He made the same mistake as Koch, only instead of calling the disease a mixed infection, his bacillus somehow became a diplococcus.

Schongolowicz undoubtedly saw the organisms in the tissue; his description of them as seen here is accurate; before I had seen the organisms in the secre-

tions and cultures I leaned toward his view, but from the description of his cultures I doubt very much whether he ever obtained a pure culture of the trachoma diplococcus.

Now, to recapitulate for the last time: The organism of trachoma is a tiny, capsulated diplococcus which is present in the trachoma nodule, which is at times, though not frequently, present in the secretions. It changes its form on different culture media and also its size. It is obtained in cultures with great difficulty, it being necessary, on an average, to inoculate nine bouillon tubes before a culture is obtained; it dies in liquid culture media in about two weeks, but lives for months on solid media.

Clinical significance of this work.—In the early stages of trachoma, and frequently even after the lapse of some time, it is often impossible by means of the methods now employed to state with certainty whether the case before us is one of that disease or not. Can a diagnosis be made with absolute positiveness? Unquestionably yes. If one can find within the secretions or in the contents of the expressed follicles an organism such as I have described, he may with absolute certainty call the disease trachoma; furthermore, he must use every precaution to prevent the patient from infecting others, for that organism, under favorable circumstances, will certainly cause the disease in others, no matter how mild a form of the disease the patient himself may exhibit. Is this method of diagnosis sufficiently reliable—can the organism be found in enough cases to render it valuable? Again, undoubtedly yes. Where one suspects trachoma there are almost invariably enlarged follicles. Squeeze out one of these follicles, smear its contents on a cover-glass, fix them in the flame, stain them by Gram's method, and if a capsulated diplococcus is present the case is undoubtedly trachoma; if it is not present the case is in all probability not trachoma.

In my series of fifty cases of trachoma, in only seventeen cases were members of the patient's family afflicted with the disease. In cases where one of a married couple had contracted the disease the other in nine cases escaped. This seems very strange, when we remember how notoriously infectious trachoma is, and how it has been known to run through camps and institutions like wild fire. There are, in the light of these investigations, several reasons for this. Where antiseptics are used the secretions soon become harmless, and may often with impunity be inoculated into other eyes; then again, the organism is very difficult to cultivate; if the soil is not favorable it soon dies. When I inoculated the human conjunctiva it was necessary to massage it into the conjunctiva; merely placing it in the sac proved of no avail. Undoubtedly the conjunctivæ of debilitated individuals, especially of such as have suffered from malaria, afford a more favorable site for growth than those of healthy people, and undoubtedly where the disease spreads rapidly it is among the former class, and from the secretions of those who have not been treated with antiseptics.

What is the period of incubation of trachoma? This is difficult to answer, even when one has watched the disease develop from day to day. The symptoms caused by the micro-organisms are certainly well marked by the end of the first week. By the end of the fifth week a diagnosis may be made from the aspect of the case.

I had now found the organism of trachoma in the tissues and secretions, had obtained it in pure culture,

had produced the disease and again obtained the diplococcus. One task remained unfinished, and that by far the most practical and important of all, i. e., the study of the toxins and antitoxins. A description of my work on this subject I reserve for a future paper; suffice it now to state that I inoculated $\frac{1}{2}$ liter of bouillon with a pure culture of the diplococcus, and allowed it to develop for ten days; this bouillon was then filtered through a Kitasato filter. This filtrate, injected into animals and human beings, causes local pain, redness and edema with a marked temperature reaction; $4\frac{1}{2}$ c.c. of this filtrate injected into the flank kills a guinea pig weighing 300 grams. If a guinea pig is treated with increasing doses of this filtrate, as fast as the temperature from the previous injection has subsided, it may receive twice the lethal dose without showing other symptoms than a temperature reaction. These facts lead me to hope that an efficient trachoma antitoxin may be found. If the action of antitoxin is, as recent investigations tend to prove, a chemic and not a biologic one, then surely a local disease like trachoma is an ideal one for the application of antitoxin.

I wish here to thank Dr. F. R. Zeit for the valuable advice and assistance which he has rendered me in the prosecution of this work.

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DISCUSSION.

Dr. GRADLE—The Doctor's work undoubtedly represents a great deal of painstaking labor, but claims of having discovered the micobe of trachoma have been put forth by others, and have never received full recognition. There can be no doubt, from a modern point of view, that trachoma is a disease due to some parasite, and the fact that so many competent observers have hitherto failed to detect the characteristic micobe should caution us against having too fervid faith in any statements.

Dr. HALE—One can hardly look at the literature without finding the enthusiasm of one day dispelled by the skepticism of the next. This is not in any sense a criticism of the writer's work, but I mention it to show that skepticism is not ill-founded. It is to be hoped that Dr. Snyder has reached a true method and has isolated the bacterium of trachoma.

Dr. GRADLE.—If I may be allowed, I will lead the discussion into another path, in which perhaps more of the members can participate on the basis of personal experience, although it is somewhat beyond the scope of Dr. Snyder's paper, viz., the clinical aspects of the difference between trachoma and follicular catarrh. First of all, we must clearly recognize the existence of follicles independent of trachoma. If Dr. Snyder can verify his claim that the micobe which he has described is characteristic of trachoma, its presence would settle the diagnosis definitely in any given case. Whenever such a micobe is present, we would necessarily have to call the disease trachoma, no matter how it appears clinically, exactly as we call a disease tubercular if the tubercle bacilli are present, no matter how different its appearances may be to the naked eye or under the microscope. But we have not yet arrived at that stage of certainty, and clinically, however, enlarged follicles can be found in a variety of conditions which have nothing to do with trachoma. First of all, in a large number of school

children we will find enlarged follicles in the lower retrotarsal fold, to a less extent on the upper lid, or in the upper retrotarsal fold. These follicles persist for months and even years without developing into any of the lesions characteristic of true trachoma, without ever involving the cornea, and without showing any progressive character. All present must have seen this condition, and know that it is sometimes very intractable to treatment, but if we relieve the refractive condition, the patient is materially improved subjectively and the follicles cease to annoy him.

We must recognize, furthermore, the existence of true follicular catarrh, not identic in any way with trachoma from a clinical point of view, the difference being one of progressiveness and the absolute immunity of the cornea in true follicular catarrh.

It is now, I think, about eighteen years since there was a moderate epidemic of this form of conjunctivitis in Chicago, especially on the North Side, where I happened to have had more patients than in other parts of the city. I had a number of cases that were slightly follicular from the start; others were not, but became follicular, most of the cases yielding, however, to applications of nitrate of silver. The follicular and non-follicular cases were due to some virus, because the affection occurred often in the same family. Three or four members of a family were affected within a short time of each other, the process of healing taking place rapidly under appropriate treatment, or sometimes without it in some cases, while in others follicular development took place. Some of the cases subsequently developed a condition which brought up the question as to how far it was identic with trachoma. I recall three cases which, after some months of neglect, presented large follicles, and which, when seen at that time, could hardly have been distinguished from true trachoma. But the subsequent history was entirely different. All these three cases I had originally seen; they had neglected themselves. They were better after a short treatment, but returned after some months, when large follicles were present. The difference between these follicles and true trachoma was this: They were situated more on the tarsal and less on the retrotarsal portion, they were never sago-like, but yet resembling in many respects the follicles seen in trachoma. All those cases were cured by a single expression, with the Knapp roller-forceps. Subsequent observation confirmed the absolute cure.

Dr. WILLIAM T. MONTGOMERY—We have all had experience similar to that related by Dr. Gradle with the follicular form of conjunctivitis, and from that fact I have been led to believe that it is an entirely distinct type of inflammation. In cases of follicular conjunctivitis I have repeatedly relieved the patient permanently of the trouble by a single expression. The cornea is never involved in that form of the disease, which is a feature very different from what we find in true trachoma.

PULMONARY TUBERCULOSIS.

ITS EARLY DIAGNOSIS AND THE LOCATING OF THE LOCAL LESION BY THE USE OF POTASSIUM IODID.

Read before the Chicago Society of Internal Medicine, Dec. 22, 1898.

BY EDWARD F. WELLS, M.D.

CHICAGO.

Cases of suspected tuberculosis of the lungs are occasionally encountered in which, from various causes, the ordinary diagnostic resources fall short of our necessities, and in which additional aids to the earliest possible diagnosis are earnestly called for. Again, there is another class of cases in which the history, symptoms and perhaps bacillary sputum may point unerringly to the presence of pulmonary tuberculosis, yet the location of the lesion can not be demonstrated, although it is desirable, or even important that this be done. In meeting these requirements iodid of potassium has a certain but not a constant value.

When iodid of potassium is administered it is eliminated, in part, by the bronchial mucous membrane, and it has long been known that, as the result of such elimination the bronchial mucus is increased, mainly by the addition of water, cough may occur or be increased, and râles may develop or be accentuated.¹

These effects are especially prone to occur when the doses of the iodid given are small or moderate. With a knowledge of these effects of the iodid of potassium Stricker suggested that the drug might be useful for diagnostic purposes in pulmonary tuberculosis, and Vetlesen² put the suggestion to a practical test. He used the iodid in $3\frac{1}{2}$ -grain doses three times a day for two or three days in 27 cases, obtaining a positive reaction in 8, and negative results in 19 cases. In the cases in which the reaction was positive, expectoration and râles were increased, the tubercular foci being readily located by the exaggerated râles heard in the vicinity.

As soon as my attention was called to Vetlesen's paper I began a series of observations for the purpose of determining, if possible, whether we have in the iodid of potassium an agent of diagnostic value in pulmonary tuberculosis, and if so, to define as far as practicable its limits of clinical usefulness. The inquiry was extended so as to include the effects of the administration of iodid of potassium upon the respiratory sounds in health and a variety of non-pulmonary diseases; in cases of non-tubercular pulmonary affections, and in cases of suspected or evident pulmonary tuberculosis. These observations have now become sufficiently numerous to permit the formation of definite conclusions, and these are here presented.

In health and in non-pulmonary diseases the iodid of potassium in small doses may produce mucous râles, but these are universally diffused, have peculiar characteristics, and can not lead the experienced auscultator astray. In some cases fine bubbling sounds may be heard at the base only with ordinary respiration, becoming audible over the upper lobes on deep inspiration. Usually cough is not present, but it developed, with any sized dose of the iodid in two of my cases. In ten carefully selected persons the iodid produced râles in only four; they were absent in six. A large number of other cases were observed with practically the same results.

In non-tubercular pulmonary affections the iodid was given in many cases with varying results. In whooping-cough the râles were not materially modified. In acute bronchitis the râles become finer and more uniform in character and distribution. In two cases of bronchitis which persisted for several weeks, with a heavy muco-purulent expectoration, with râles only on forced breathing or coughing, diffused fine bubbling appeared with gradual disappearance of the coarse crackling râles. In one case of hay-fever the râles were not changed. In all of a considerable number of cases of asthma the sonorous and creaking râles gave way to a fine bubbling, or in a few days to the entire disappearance of all morbid sounds. In all the cases of this class the iodid appeared to produce moist râles or modify the morbid sounds present in a large proportion of instances.

It is, however, the effect of iodid of potassium on the respiratory sounds in persons with demonstrable or suspected pulmonary tuberculosis, which is of peculiar interest and importance in this study. Generally speaking, it may be affirmed that in these cases in which tuberculosis is proven to exist, but with inability to locate the lesion, the locality and extent of the affected area may be made evident by the development of râles; that in cases with râles and an apparent ability to demonstrate the extent of local involvement,

¹ Trousseau: Clin. Med., Phila., 1873, ii, 167; Brunton: Pharmacology, etc., Phila., 1885, 519.

² Norsk. Mag. f. Lag., October, 1897.