BACTERIOLOGICAL AND EXPERIMENTAL OBSERVATIONS ON FOCAL INFECTIONS *

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For a number of years observations have been carried on, in connection with the clinic of Dr. Frank Billings, at Rush Medical College, with reference especially to chronic focal infections and associated systemic disease. The more general features and the therapeutic results of this work are presented in the preceding article by Dr. Billings. Here will be given chiefly some bacteriologic and experimental data derived largely from a study of cases which came under his observation.

Some of the first work undertaken had to do with genito-urinary disease and chiefly with infections of the urinary bladder by bacteria of the colon group. From the study of many organisms of this variety it has been found that they vary, to a certain extent, both in morphology and in cultural reactions. Some are short and plump; others slender and long. All are Gram-negative. Some grow profusely on ordinary media, others give a scant growth. A few varieties were found to grow, at least when first isolated, better under anaerobic conditions than aerobic; none are strictly anaerobes; all produce indol and all acidify milk permanently, and with few exceptions coagulate it after from twenty-four to seventy-two hours. They vary much in the rapidity with which they ferment sugars; they produce gas in glucose, saccharose, lactose and mannite. By blood-agar plate cultures they may be divided into two distinct groups, hemolytic and non-hemolytic. The latter are more common. Careful observations of a large number of strains have thus far revealed no change on cultivation with respect to hemolysis, though such changes without doubt have been observed by others. Hemolytic and non-hemolytic varieties may show no other differences. In most instances the colon bacilli exist pure. In two cases, both with hemorrhage from the kidney, *B. coli* was mixed, in one case with a Gram-positive coccus which simulated a staphylococcus but which refused to grow in various media under either aerobic or anaerobic conditions; in the other, with a long unbranched thread-like Gram-positive bacillus which grew well but slowly on sugar media and which frequently formed tangled masses. This mixed flora was observed repeatedly in both cases for a period of many months without any appreciable alterations.

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The infections of the bladder and prostate were associated with a variety of clinical conditions, including joint-lesions, neuritis, anemia, pyelitis, etc. Often the patients were also neurasthenic. Blood-cultures and cultures from joint-fluids, when possible to obtain, have never given positive results. This fact inclines one to assume that absorbed toxic substances are responsible for the general symptoms.

Some interesting points have appeared in connection with the study of the serum in some of the cases. Many do not reveal, at least to any extent, the presence of specific antibodies in the blood. In others (four cases) there was distinct evidence that the serum of the patient was less lytic to the homologous organism than normal serum. For instance, in one case in which the patient gave a history of urinary infection for many years associated with hemorrhage from the right kidney, the serum had little or no destructive action on the infecting bacillus, whereas normal serum was highly bactericidal. The agglutinating power was *nil* and the opsonic content, at first low, became high after treatment with the killed bacillus. This loss of specific lytic power of the patients' serum is interesting and deserves further study, especially in chronic infections with organisms of this and related groups. The facts in such cases can best be explained by assuming that the microbe, gaining access to the individual, causes specific reactions in the serum, to meet which the microbe specifically adapts itself. The microbe thus immunizes itself against an abnormal individual and may be still susceptible to the serum of a normal person. This reciprocal adaptation continuing for a long period of time may give rise to profound changes on the part of both microbe and host.

In this connection should be mentioned some cases of urinary infection caused by a bacillus growing pure and apparently belonging to the hemophilic group. A detailed report of these has been given in a previous article.¹ All attempts to grow the bacillus on media other than that containing hemoglobin persistently failed. Its growth is scant and better anaerobically than aerobically. It is a small, Gram-negative, non-motile bacillus and is distinctly, though not strongly, hemolytic in blood-media. It differs from the influenza bacillus in being hemolytic, in not showing any evidence of symbiosis with other germs and also in some of its morphological features. In two cases in which it was found the patients suffered from joint trouble at the time or previously, but whether or not it had any causal relationship could not be definitely decided. It was non-pathogenic for animals.²

1. Davis: Jour. Infect. Dis., 1910, vii, 599.

2. Since this article was written, C. Koch (Ztschr. f. Geburtsh. u. Gynäkol., 1912, lxi, 634) has described an apparently identical hemophilic bacillus which he isolated from two cases of puerperal fever. This bacillus appeared in pure culture in the lochia at a time when the fever was at its height and for this reason he believes it was the causative organism.

Considerable attention, especially of late, is being given to focal infections about the mouth, nose, throat, teeth, ear and tonsils. The last-mentioned have, indeed, for many years been the object of attack and there is little doubt but that they deserve all the blame that they have received. It is probably true, however, that the other foci mentioned have not been sufficiently emphasized and I think this is especially the case as regards lesions about the teeth and jaws. This subject is discussed in the accompanying article by Dr. Gilmer, in which the relation of such lesions to general or systemic conditions, such as anemia, gastro-intestinal disturbances, arthritis, etc., is clearly set forth and its frequency emphasized. My own observations along this line have been limited. Pyemia, septicemia, meningitis, neuritis, endocarditis, etc., as acute infections originating from alveolar abscesses and infected foci about the teeth, are well-known occurrences. Chronic generalized or systemic infections are rarer and less commonly recognized. As an illustration of the latter I may mention briefly one rather striking case which came under observation.

A young man had been suffering for several weeks with symptoms of severe multiple neuritis associated with some anemia, marked emaciation and slight fever. The joints were not involved and physical examination revealed no heart lesion. For a long time the patient had been troubled with severe pyorrhea and at the time of examination the gums of the lower jaw were red and swollen, bled easily and on pressure abundant pus exuded from between the teeth and gums. Smear and culture examination of this pus revealed, in nearly pure growth, many Gram-positive diplococci resembling pneumococci. The colonies produced a green zone on blood-agar and the organism acidified and coagulated milk and fermented inulin. A blood-culture made by taking several cubic centimeters of blood from the vein at the elbow yielded in each of three inoculated culture-tubes a pure growth of the same diplococcus. In animals this organism was not highly pathogenic. One broth-culture intraperitoneally would kill guinea-pigs in twenty-four to forty-eight hours. Two rabbits were inoculated repeatedly with large amounts of culture without manifesting serious or fatal effects. Apparently these diplococci are identical with the cocci often found in endocarditis and called endocarditic cocci and they are also probably identical with the diplococcus almost constantly found about the mouth and usually called *Streptococcus viridans* (Schottmüller). I may say, too, that they appear to be the same as the diplococci which I have found at times in the tonsillar crypts especially in cases of endocarditis and which I will discuss later in the paper. In this particular case the tonsils were carefully examined and appeared to be normal and no suspicious foci of infection other than the teeth could be held accountable for the condition. Unfortunately, the patient did not remain long under observation and the termination is not known.

The fact that focal infections of tonsils frequently become general and localize in various parts and organs of the body is a subject which seems to be attracting more attention from year to year. Clinically the relation between anginas and certain lesions like acute articular rheumatism and endocarditis has long been suspected and more recently kidney and other lesions have been noted as not infrequent complications of primary tonsillar infections. Such complicating lesions may be acute, subacute or chronic. About two years ago³ I published a preliminary statement of some bacteriological and experimental observations with bacteria isolated from tonsils excised from a variety of clinical conditions including chronic and recurrent arthritis, endocarditis, nephritis, recurring tonsillitis, neuritis, etc. Since that time many more cases have been studied and some further facts have been noted which seem worthy of record.

The clinical features of cases of this type indicate beyond doubt the presence of invading organisms or their toxic products. That such cases associated with diseased tonsils may often be influenced favorably by extirpation of these organs has been noted by many clinicians. The bacteriology, however, especially of the subacute and chronic systemic conditions, is in many respects incomplete and the literature abounds in general and indefinite statements about the variety of bacteria in the tonsils. Work along this line has largely been the examination of swabs and smears made directly from the surface of the tonsils *in situ*. This surface is necessarily contaminated by bacteria from the mouth, throat, nose, food, etc., and the great variety of bacteria reported to have been found here is thus at least partly explained. It is evident, too, that the bacterial flora on the surface may be very different from that in the crypts and some preliminary work on cultures taken from the surfaces and from the crypts of the same tonsils convinced me that this was an important point. Consequently, in the study of tonsils, in practically all cases the cultures have been made from the surface and from the crypts of the extirpated tonsils and, in many instances, cultures were also taken from the tonsillar surface before excision and compared with those taken after. In order to obtain cultures from the crypts the tonsils, as soon after excision as possible, were incised with a hot knife, thus exposing the depths of the crypts from which these smears and cultures were made. In all cases the blood-agar plate method was used.

The tonsils, as stated above, came from a variety of clinical conditions which may be conveniently divided into four groups, namely, arthritides, nephritides, cardiac lesions and recurring and chronic tonsillitis. The tonsils were usually hypertrophied but not in all cases. In some instances in all groups they were normal in size or sometimes, indeed, atrophic.

3. Davis: Jour. Am. Med. Assn., 1910, lv, 26.

Many were submerged and when excised were found to be diseased and much larger than they appeared on simple inspection. Their surfaces varied, being at times deep red or purplish-red and irregular; often they were smooth and coarsely lobular. In cases with a history of repeated tonsillitis the connective tissue capsule and the septa were thickened and the crypts were often distorted. The latter frequently contained small, globular, cheesy, foul-smelling masses. In microscopic sections are often seen deep down in the crypts small aggregations of leukocytes in which cocci may be found in suitably stained preparations. They are rarely found beneath the epithelium. At times the crypts are crowded with pus-cells but this is not common in the chronic cases. Plasma-cells are found in abundance beneath the epithelium and especially about the small blood-vessels. It should be stated that they are always found in the tonsils after the first few weeks of life regardless of the anatomic condition, but in hypertrophied and diseased tonsils they are as a rule more numerous. Giant-cells are sometimes found about cholesterol crystals and débris and should not be mistaken for tuberculous giant-cells. Cross-sections of small solid epithelial masses often resemble giant-cells also.

The results of culture inoculations from the tonsils of the various groups may be briefly summarized as follows: In twenty-eight cases of arthritis hemolytic streptococci were obtained in all and were predominant in twenty-five. In many cases the growth was practically pure. In two cases the pneumococcus was predominant and in one case the *Streptococcus mucosus* occurred together with a few hemolytic streptococci. These cases of arthritis include a variety of joint-lesions ranging from simple joint-pains associated with tonsillitis to severe chronic joint-involvement. In some instances the arthritis was deforming in character and associated at times with exudates into the joints. The joint-fluids and blood from these cases were invariably sterile.

The tonsils from ten cases of nephritis were examined and hemolytic streptococci were found pure or predominant in the crypts in nine. In one case a small Gram-positive bacillus in nearly pure growth was found but was not identified. These cases of nephritis were subacute or chronic and several patients had developed nephritis shortly after having had colds or tonsillitis. Some were mild, others severe, and two were hemorrhagic in character.

The tonsils from a series of patients with definite heart lesions were examined following extirpation with interesting results. Nearly all were at the time suffering from arthritis or gave histories of having had it in the past and they suffered also from recurrent attacks of tonsillitis. Two cases were malignant in character; the others were relatively mild. Hemolytic streptococci were found in six and were far more numerous than any other organism. In the remaining four, pneumococci appeared

in predominating numbers and in two they were nearly pure. In one case of fatal malignant endocarditis with pneumococci in the blood and in the pleural and pericardial exudates, the tonsils were only slightly enlarged but near the base they were very fibrous and in the depths contained small pockets filled with pus-cells and diplococci. In the cultures from the crypts pneumococcus-like organisms grew almost pure, there being a few hemolytic streptococci.

The extirpated tonsils from sixty-one cases of tonsillar hypertrophy and chronic tonsillitis in which no marked systemic disease existed were examined. In fifty, hemolytic streptococci were found in large and usually predominating numbers and often practically in pure growth. *Streptococcus mucosus* was found in large numbers in one case and in six the white staphylococcus was more numerous than any other organism. In two cases the pneumococcus predominated and were mixed with a few hemolytic streptococci. In three instances *B. influenzae* was found in large numbers.

The streptococci isolated from the various groups could not be differentiated. They were all hemolytic on blood-agar plates and they acidified and nearly always coagulated milk. The zone of hemolysis varied considerably, most of the strains producing a wide clear area about the gray colonies; a few strains gave a smaller and a slightly turbid zone and grew usually less luxuriantly. They do not differ in their sugar or milk reactions or in their pathogenic properties for animals.

Forty-three strains isolated from the tonsillar crypts from the various clinical groups were tested on the following sugars: dextrose, lactose, mannite, raffinose and inulin. Briefly, they all formed acid in dextrose and none in raffinose and inulin. All but five fermented lactose, one of these strains coming from a case of arthritis, the other four from cases of recurrent tonsillitis. Eleven strains fermented mannite and thirty-two did not. The grouping into mannite and non-mannite fermenters has no evident relation whatever to the clinical condition. For instance, some streptococci isolated from arthritis cases fermented mannite; others did not; and the same is true with reference to the other groups. When compared with streptococci from other sources (puerperal fever, erysipelas, empyema, scarlet fever) they show no essential morphological or cultural differences.

The organisms referred to in this paper as pneumococci are Gram-positive, lanceolate diplococci and produce a green zone on blood-agar plates. In liquid cultures they grow in long chains. Some ferment inulin and others do not; all ferment dextrose and lactose and none ferment mannite and raffinose. These organisms are commonly called *Streptococcus viridans* (Schottmüller), but I think their more important morphological features and cultural reactions justify one in placing them in the pneumococcus rather than in the streptococcus group. Organisms of

this type are found normally on the buccal mucosa and especially on the surface of the tonsils. From the many examinations made it appears that they are not commonly found in the crypts except in some cases of endocarditis in which they were found predominant in four of ten cases. This is interesting in view of the fact that what appears to be an identical organism is often found in the blood and on the heart-valves in cases of endocarditis. More data are desired in order to confirm this point, but it appears that the atrium of infection for these germs in such cases may well be the tonsils. These cocci, it may be pointed out, are not the same as those found in the tonsils in acute arthritis, which are apparently typical hemolytic streptococci. For this reason, when found in the blood in cases of endocarditis following rheumatism, as often happens, these pneumococci should be looked on as probable secondary invaders localizing in the heart-valves, which were perhaps injured during an earlier infection.

Attention should be called to the striking difference that exists between the surface and the crypt flora in tonsils. Invariably, on the surface, organisms of the pneumococcus type are found in large and predominating numbers but mixed with a variety of other bacteria. Often a few hemolytic streptococci may be found here in the more or less chronic cases. In acute infections of the tonsils, however, like diphtheria and acute streptococcic tonsillitis, which primarily involve the surface of the tonsils, naturally the causal organisms will then predominate, though even there the normal pneumococcus-like bacteria may be found in abundance on the culture-plates. The presence normally of these surface diplococci so similar to pneumococci is a fact that should always be kept in mind in examining throat cultures. Many diagnoses of the so-called pneumococcus throats have been based, no doubt, on the presence of these diplococci. The crypts, on the other hand, as shown by the data presented above, contain in most cases hemolytic streptococci in large numbers often nearly pure, and only occasionally, and probably only in certain diseased conditions, do pneumococci invade tonsillar crypts.

Strains of organisms from the various clinical groups were inoculated into animals and the results are as follows: Seventeen rabbits were inoculated with hemolytic streptococci from the arthritic group; fifteen developed multiple arthritis and one developed acute endocarditis. Five strains of pneumococci were tested and in one case mono-articular arthritis appeared; no endocarditis. Eight strains of streptococci from the nephritic group injected into rabbits caused arthritis in all. Four strains of streptococci from endocarditic cases caused arthritis in all, but no endocarditis; three pneumococcus strains from this group caused endocarditis in two animals but no other lesion. Seven strains of hemol-

ytic streptococci from cases of chronic or recurrent tonsillitis caused arthritis in all; four strains of pneumococcus gave negative results. The hemolytic streptococci are virulent for guinea-pigs and a strain which had produced arthritis in a rabbit, on intracardiac injection into a monkey (*Macacus rhesus*), caused multiple arthritis. The animal died after about two weeks and the cocci were recovered pure from the joints and heart's blood.

The arthritis caused in animals by the streptococci is manifested by lameness and swelling of the joints and usually appears from the third to the fifth day after inoculation. On the whole, the various strains isolated from the tonsils are quite uniform in their pathogenic properties, a given dose in animals of uniform size usually producing similar results. Some of the animals die in the course of one to three weeks but in many the joint-lesions gradually subside and the animal recovers. In less severe cases few joints or only one may be involved but usually the arthritis is multiple and in some rabbits almost every joint in the body was attacked including the vertebral joints. The carpal joints and the joints of the hind limbs are often the seat of localization and, on the whole, the various joints of the fore and hind limbs are about equally involved. In a number of animals the process became chronic, the joints increasing in size with marked destruction of bone and joint-surfaces. In one case subluxation occurred after six weeks. Chronic joint-abscesses may arise in which streptococci in small numbers may be found in the glairy mucoid or mucopurulent contents and such animals often live for months gradually becoming emaciated and badly crippled but nevertheless appearing quite lively and eating normally. Ultimately most of them die but usually without septicemia. A few streptococci may be found in the chronic lesions, though in some instances the cultures remained sterile. In four animals, following non-fatal injections, the joints simulated a deforming arthritis. They became large and exostoses appeared about the end of the bones. After several months the deformities in these cases gradually, and apparently entirely, disappeared.

Post-mortem examination of the animals revealed the fact that not infrequently in the early stages the involvement is peri-articular and often extends to the tendon-sheaths. At times, especially in the hind limbs, a tendon-sheath might be involved throughout its entire length and the joint-cavities remain entirely free. Microscopic examination of sections through these involved extremities have been made in some of the animals. It would appear from the data at hand that the organisms first localize in the subserous structures about the joints, forming small infected foci which later break into the cavities. The exudate in the joints early is glairy and mucoid, but soon becomes purulent and contains large numbers of polynuclear cells and streptococci. Usually abundant

phagocytosis of this organism in the exudate is noted. After a week or longer in some rabbits, but not in all, the exudate may become thick and pasty. Streptococci can ordinarily be readily grown from these joint-exudates, but a few exceptions have been noted. In one case, in an animal that died on the fifth day with definite arthritis, the cocci could be seen in the leukocytes; but careful cultures on blood-media gave no growth. In two other instances, though the involvement of the joint was unmistakable, no organisms grew in the cultures.

In the bodies of the inoculated animals careful search was made for other lesions, especially endocarditis. In only one instance following inoculation with hemolytic streptococci was a lesion found, vegetative in character, on the tricuspid valve. This was not extensive, but was definite and was produced by a strain isolated originally from the crypts of tonsils in a case of multiple arthritis. The joints of the animal were also involved, but there was no other localization. The organisms were recovered from the heart's blood. Pericarditis was not found in any instance.

As stated above, in two instances pneumococci produced an endocarditis. In one case by intracardiac injection a very extensive mitral endocarditis developed in an animal associated with typical large renal infarcts and septicemia, but without joint-lesions. This organism, which fermented inulin and gave the typical green zone on blood-agar, was isolated from the depth of a tonsil from a case of severe multiple arthritis, not associated at the time, so far as could be determined clinically, with heart lesions. In this case also streptococci were abundant in the tonsils, and on intravenous inoculation into an animal produced arthritis. In the second case a definite but less extensive mitral endocarditis was produced by intravenous injection with a pneumococcus from the crypts of the tonsils in a case of recurrent tonsillitis associated with endocarditis. From the valvular lesions the organism was recovered pure. It did not, even in huge doses, produce arthritis in animals.

The mere fact that the various strains of streptococci from tonsils can cause joint-lesions in animals is perhaps in itself not of great significance. It has been shown by Cole, Harris, Beattie and others that streptococci from various sources will produce arthritis in animals. Indeed, hemolytic streptococci from the normal throat may do so, as I have myself demonstrated. It is therefore not surprising that strains from the various clinical groups appear to be identical and behave alike when injected into animals. It is possible that the reason why in one individual streptococci causes arthritis, and in another nephritis lies in the varying local susceptibility of the organs of the individual rather than in any peculiar specificity of the infecting cocci.

The therapeutic results following tonsil extirpation in this series of cases are, on the whole, distinctly favorable. Other observers⁴ have obtained similar results in arthritis, nephritis, heart lesions, toxemias, etc. The therapeutic results probably furnish the best argument we have, at present at least, in favor of the idea that the cause of these systemic conditions lies in infected tonsils. Since in such infected tonsils there are found so often virulent hemolytic streptococci, an organism as we know prone to attack serous surfaces generally, and no evidence, so far as our present technical methods indicate, of any other significant germ, one would seem justified in at least considering this organism a very suspicious etiological agent.

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3. Curschmann and Schichhold: München. med. Wehnschr., 1910, lvii, 281.