IS DIPHTHERIA FREQUENTLY A BACTEREMIA? *

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In August last, Conradi and Bierast¹ of the Hygienic Institute of the University of Halle reported the results of an extensive examination of the urine of diphtheria patients. They call attention to the fact, that, while diphtheria has been regarded as essentially a local disease, yet the Loeffler bacillus has frequently been isolated from the blood and organs after death, and occasionally from the blood during life, usually, however, in the agonal stage of the disease. On account of the technical and other difficulties of obtaining a sufficiently large quantity of blood from diphtheria patients, they sought to solve the question of diphtheria bacteremia by an indirect method, namely, an examination of the urine of those actively ill, and of convalescents. In all, 155 patients were examined, of whom fifty-four showed a positive urine. In six cases only, however, were virulence tests made, all of which proved positive. As the material was sent to the research laboratory at random, there was no possibility of following up a given case in order to study the question of the persistence of the bacilli by repeated examination. Of the 54 positive cases, 32 were female and 22 male; 36 children, 18 adults. Thirty-one urines were taken in the first week of illness, 10 in the second, 5 in the third, and 2 in the fourth. One was found positive in the ninth week of convalescence. The urine, 20 to 30 c.c. in amount, was taken by means of a sterile catheter with every precaution against contamination, and the centrifugalized sediment spread over one or two Loeffler plates and plates of Conradi and Troch. Both Loeffler and Neisser's stain were used for identification. The bacteria were found in normal as well as albuminous urine, showing that they pass through healthy as well as diseased kidneys. In most cases they were very few in number.

No clinical data are furnished in regard to the severity or outcome of the cases giving positive results. On the strength of their findings the authors make a plea for the disinfection of the urine of convalescents, until, by three negative cultures, it is shown to be free from diphtheria bacilli. They suggest that diphtheria of the skin and mucous membrane, which shows such a predilection for the genital and anal regions, is due to direct infection from the urine, and that the mystery that surrounds

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1. Conradi, H. and Bierast: *Deutsch. med. Wehnschr.*, Aug. 22, 1912, No. 34.

the origin of certain local epidemics of diphtheria may be explained in the same way.

Dr. R. Koch² of Frankfort, in December, reports the results of his examination of 111 urines from 26 patients. In 4 of these, which came from two patients, virulent diphtheria bacilli were found. In 10 urines from 5 other patients, diphtheria-like bacilli were found, which either could not be isolated in pure culture or else proved to be avirulent. In the original smears diphtheria bacilli were never recognized.

The urine was passed into a sterile vessel after thorough cleansing of the meatus with mercuric chlorid solution. In 74 examinations made on 19 patients suffering from mild or moderately severe diphtheria—in one case 14 examinations were made in 25 days—no suspicious organisms were found. In 5 other patients diphtheria-like organisms were found which proved to be avirulent; 2 of these were fatal cases. Post mortem examination of the urine proved negative.

Of the two positive cases, both ended fatally from the toxemia of the disease and cardiac paralysis. The first showed negative urine on the first two examinations, virulent diphtheria bacilli being found on the seventh day, the patient dying on the following day. In the second case they were found on the fifth day of the disease and the following day, being absent on the next five days and present on the twelfth day again, the patient dying the next day. The appearance of the bacilli in the urine was in neither case coincident with change in the general symptoms. The presence or absence of albumin in the urine had no bearing on the presence of bacilli.

Nineteen cases of scarlet fever complicated by diphtheria were examined as controls. In four of them the urine contained diphtheria-like bacilli which proved to be avirulent. We believe that only animal tests can be relied on for the identification of diphtheria-like bacilli in the urine. While Loeffler bacilli may occasionally occur in very severe cases, the fact is not of practical interest, as such patients, being confined strictly to bed, would not be likely to be a source of danger through infected urine.

The latest writer on the subject is Walter Beyer³ of Rostock, whose reported results are little short of startling. He examined nineteen cases of diphtheria daily, or every second day, from the active stage of the disease to late convalescence. Forty c.c. or more urine were taken with proper precaution against contamination, and the centrifugalized sediment poured over a Loeffler plate. Practically every urine examined showed diphtheria bacilli at each examination; their number being greatest during the active stage of the disease and gradually diminishing.

2. Koch, R.: *Deutsch. med. Wehnschr.*, Dec. 12, 1912, No. 50.

3. Beyer, Walter: *München. med. Wehnschr.*, Feb. 4, 1913, No. 5.

In the case of eight convalescents, four of whom had recovered from their illness, three and one-quarter to three and one-half months previously, and the others eight, six, five and four weeks, respectively, the urine showed the continued presence of diphtheria bacilli, six strains of which were said to have been virulent for guinea-pigs, the other two avirulent. In all of the eight cases cultures from the tonsillar crypts showed diphtheria bacilli. It is to be noted that there is nothing said by Beyer or Conradi as to their methods of testing for virulence; that is, as to whether antitoxin was used in the test.

Beyer believes that it has been established beyond doubt that in the early stages of diphtheria, at least, the disease is essentially a bacteremia. Whether the organisms found in convalescents constitute also an evidence of a continued blood-infection he does not undertake to say.

Our series of cases comprises 54 patients with 56 examinations of urine. These were divided into three groups roughly corresponding to the type of disease which characterize the clinical material from which the three observers quoted obtained positive results. Thus the first group, 25 in number, consisted of routine cases; the second, 21 in number, cases of the severer type with a great deal of membrane and showing symptoms of toxemia; third, 8 in number, cases of recent convalescents. All were patients at the Willard Parker Hospital.

In the first group, there were 5 adults and 21 children, the ages of the latter ranging from 2 to 13 years. There were 18 males and 7 females. Twelve patients were in the first week of the disease, 7 in the second, 3 in the third, 1 in the sixth week and 2 not determined. Only 1 or 2 of these cases were of any severity. The urine proved negative in every case.

In the second group of 21 cases there were 4 adults and 17 children, the latter 2 to 11 years, 16 males and 5 females. Twenty were ill for a week or less at the time of taking the urine and 1 with croup and cervical adenitis for sixteen days. Two of this group proved positive. One, Edward M., 8 years of age, two days ill, had thick membrane covering the tonsils, fauces, uvula and posterior walls of the pharynx; there was also nasal discharge and marked toxemia. The serum tube and ascitic broth showed Loeffler bacilli which proved to be virulent. A specimen taken one week later was negative. The patient made an uneventful recovery. A second patient, Sam G., aged 5 years, had been ill three days. The patient had thick membrane on both tonsils, uvula and pharynx with profuse purulent nasal discharge. The cervical nodes were swollen and the patient very toxic. The serum tube and broth showed virulent Loeffler bacilli. The second specimen, taken eight days later, proved negative. Neither of these patients were catheterized on either occasion. Of the remainder of this group, from one, Hoffman's bacillus

was isolated, and from a case of diphtheria complicating scarlet fever and sepsis a specimen taken by catheter showed diphtheria-like bacilli, which, however, proved not to be diphtheria. All the other cases were negative.

TECHNIC

In the first two groups the female patients were catheterized, 20 or more c.c. of urine being drawn into a sterile centrifuge tube. In the case of males the first part of the urine was discarded and the residue passed into sterile centrifuge tubes through a sterile glass funnel. In one or two instances very young males were catheterized. In three cases only 8 to 12 c.c. of urine was obtained. The centrifugalized sediment was treated as follows:

One c.c. was drawn off by pipet, 0.8 of which was put into 3 to 4 c.c. of ascitic broth and the remaining 0.2 poured over a Loeffler serum tube and incubated. Colonies developing on the tube were examined in the routine way, and if any pellicle developed on the broth, it was stained with Loeffler's methylene blue and examined.

In the third group, although we had every confidence in our technic in producing equally if not more definite results than theirs, it was thought advisable to follow exactly that of the three writers quoted. The patients were catheterized after thorough cleansing of the meatus with mercuric chlorid solution and 35 to 40 c.c. of urine drawn into a sterile container. The centrifugalized sediment with 1 c.c. of the urine was drawn off by pipet and one-half of the quantity allowed to flow over each of two Loeffler plates previously tested with a known strain of Loeffler bacillus. In addition, in four cases 5 c.c. of the remaining urine was put into 75 c.c. of ascitic broth.

In this group there were eight patients, five of whom were females, five children and three adults. With one exception, they were all cases of clinical diphtheria of a pronounced type; the exception was a case which showed only a markedly congested pharynx from which cultures taken on several different days showed typical diphtheria bacilli. The patients had been ill from three to twelve days and were mostly afebrile at the time of the test. All showed the presence of diphtheria bacilli on culture in the throat.

In three cases there was no growth on the plates after twenty-four hours; in the other five, only colonies of cocci were present, probably staphylococci. The ascitic broth also proved negative.

CONCLUSIONS

The two positive findings in our series may well have been due to accidental contamination at the time of taking the urine, especially as a catheter was not made use of in either case. We conclude, therefore, that diphtheria bacilli may occasionally gain access to the blood and be

excreted in the urine in very severe cases of diphtheria with marked ulceration of the mucous membrane of the pharynx and tonsils. This fact is of theoretic interest, but of little practical importance to the physician. Finally, we believe that identification of diphtheria bacilli in the urine should not rest on morphologic characteristics alone, but be confirmed by isolation and animal inoculation controlled by the use of diphtheria antitoxin.