

ON THE VALUE OF UROTROPIN AS A URINARY ANTI-
SEPTIC WITH ESPECIAL REFERENCE TO ITS
USE IN TYPHOID FEVER.*

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In a previous number of this Journal† the writer published an article "Upon the Presence of the Typhoid Bacillus in the Urine," and, as the result of observations upon 38 cases of typhoid fever, drew the following conclusions: (1) Typhoid bacilli were demonstrated in 9 out of the 38 cases (about 25 per cent). (2) The bacilli, when demonstrated, were always present in large numbers, and in practically pure culture. (3) The bacilli appeared first in the later stages of the disease, and persisted, in the great majority of cases, far into convalescence. The urine of typhoid patients should, therefore, not only be rigorously disinfected during the disease, but should also be carefully supervised during convalescence. (4) The typhoid bacilli were practically always associated with albuminuria and the presence of renal casts. On the other hand, urines containing considerable amounts of albumin and casts in large numbers often showed no typhoid bacilli. (5) Irrigation of the bladder with antiseptic solutions offers a possible means for removing permanently the bacilli from the urine.

Since the publication of that article two further contributions to the subject have come to my notice, the first by Horton-Smith and the second by Petruschky. The work of Horton-Smith appeared in 1897 in the *Transactions of the Medical and Surgical Society* of London, and should properly have been included in the literature mentioned in my previous article. Horton-Smith examined the urines

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† *Journal of Experimental Medicine*, 1898, iii, 349.

of 7 typhoid patients, with 3 positive results. His conclusions were in general very similar to mine. Horton-Smith also pointed out the fact that the typhoid bacilli can be demonstrated oftentimes in cover-glass preparations from the urine; and, further, that the organisms may be so numerous as to render the urine distinctly turbid.

Petruschky* examined the urines of 50 typhoid patients with but three positive results. Petruschky followed the cases into convalescence, and found that the first case retained the bacilli two months after the temperature had reached the normal point; that in the second case the bacilli were still present a month and a half after the disappearance of fever; that in the third case the organisms had disappeared eight days after the beginning of convalescence. The fact that the organisms were present in enormous numbers was strongly emphasized by Petruschky. According to his calculation a single cubic centimetre of urine, in one case, contained 170,000,000 typhoid bacilli.

Finally, through the courtesy of Dr. Harvey Cushing, I am permitted to report briefly a most remarkable case observed recently at the Johns Hopkins Hospital. The patient, a man, had been in the Johns Hopkins Hospital five years before with an attack of typhoid fever. Ever since his discharge from the hospital he had had trouble with his urine. Investigation showed him to be suffering from a cystitis, and the typhoid bacillus was obtained in pure culture from his urine.

We see, therefore, in the light of the accumulated evidence, that our supervision of patients sick with typhoid fever has hitherto been very inadequate; that we must disinfect carefully the urines as well as the stools of typhoid patients; that the necessity for such disinfection and supervision does not cease with the fever, but must be kept up, oftentimes for weeks and sometimes for years.

In the previous article already referred to, the question of treatment for this condition was barely touched upon. In a single case the bladder was irrigated with antiseptic solutions, and the results demonstrated the comparative uselessness, as a remedy, of boric acid, and the effectiveness of corrosive sublimate. Irrigation, however, with its necessary catheterization, is not a method of treatment easily

* *Centralbl. f. Bakt.*, 1898, xxiii, 577.

applicable, and it was next determined to try the effect of the so-called urinary antiseptics, salol, benzoate of ammonia, urotropin, etc., given internally.

The number of cases of typhoid fever comprised in the present series is 66, and the number of specimens of urine examined 190. Of the 66 cases, 14 showed the presence of typhoid bacilli in the urine. The percentage of positive results is therefore somewhat smaller than in the previous series, a difference due possibly to the fact that, in the latter series, the urines were first examined at or about the beginning of convalescence; whereas, in the former, investigation was begun early in the disease. For this reason it is entirely possible that in a number of cases the urines had contained bacilli, but that these had disappeared spontaneously before investigation was begun. Every case showed at some time during the disease a positive typhoid serum reaction (Widal).

The methods employed in obtaining the urines, and the tests applied in the identification of the typhoid cultures, were the same as in the previous series.*

The positive cases, their course and treatment, may be outlined briefly as follows:

Case VIII. Clinical course severe. Relapse. Urine was examined on the 39th, 46th, 50th, 53rd, 57th, and 61st days. Salol was given, 10 grs. t. i. d. from the 42nd to the 55th day. The bacilli persisted, however, in large numbers, and the patient left the hospital with the condition unrelieved.

Case IX. Clinical course very mild. Bacilli present in the urine of 22nd and 28th days. The number of organisms was always small. Treatment: salol 10 grs. t. i. d. from the 26th to the 35th day. Urine of the 32nd and 35th days showed no bacilli.

Case X. Clinical course very severe. Relapse with streptococcus infection. Death. Bacilli present in urine in very large numbers on the 19th, 25th, 43rd, 76th, and 79th days. No treatment was instituted in this case.

Case XVI. Clinical course very severe, followed by cholecystitis. Cholecystotomy was performed and many stones of considerable size evacuated. Fluid from the gall bladder showed typhoid bacilli in pure

* Loc. cit.

culture. In this case salol was given in 10 grain doses three times a day from the 28th to the 35th day. The urine became dark on standing. In spite of the treatment, however, typhoid bacilli were found in large numbers in the urines of the 28th, 35th, 39th, and 43rd days. At the suggestion of Dr. H. F. Vickery it was then resolved to try urotropin, and the drug was given in doses of 10 grains three times daily from the 45th to the 54th day. Further examination of the urine was made on the 47th, 49th, 52nd, 57th, and 71st days, and not a typhoid bacillus could be demonstrated. Moreover, it is to be noted that upon the day of the last examination (71st day) 17 days had elapsed since the last dose of urotropin. The removal of the bacilli was, therefore, permanent, and not confined merely to the time during which the drug was administered.

Case XV. Clinical course moderately severe. Typhoid bacilli were found in large numbers on the 32nd day. Urotropin, 10 grains t. i. d., was given from the 33rd to the 38th day, and from the 45th to the 53rd day. The urines of the 35th, 38th, 45th, 53rd, and 67th days showed no typhoid bacilli. After 50 grains of urotropin the bacilli had disappeared, and two weeks after the administration of the drug had been stopped no bacilli had reappeared.

Case XXV. Clinical course very severe. Death. Typhoid bacilli found in urine of the 15th day. Case not treated.

Case XXVIII. Clinical course moderately severe. Typhoid bacilli in very large numbers found in urines of 34th and 38th days. Urotropin, 10 grains t. i. d., was given from the 38th to the 42nd day. On the 40th day no bacilli could be found—a fact which is the more remarkable when it is noted that the patient vomited four of the five doses given. The amount of urotropin actually absorbed must have been very small, still its action was effective. On the 47th day—5 days after urotropin was stopped—no bacilli had reappeared in the urine, and a similar result was obtained upon the 108th day.

Case XXXIII. Clinical course moderately severe. Typhoid bacilli present in large numbers on the 25th day. Urotropin, 10 grains t. i. d., was given from the 26th to the 27th day. On the 27th day, after only 20 grains had been given, the bacilli had disappeared. Further examination on the 70th day showed no bacilli.

Case XXXIV. Clinical course moderately severe. Bacilli present in urines of the 12th and 13th days in large numbers. Urotropin, 10 grains t. i. d., from the 13th to the 16th day. On the 14th day, after 30 grains of the drug, the bacilli had not entirely disappeared, but the number

had been reduced from millions to hundreds per cubic centimetre. On the 15th day, after 60 grains of urotropin, no bacilli were seen. On the 20th day there was also a negative result. On the 38th day, however, I was much surprised to find that, not only had the bacilli returned to the urine, but there was also a mild cystitis—a condition which had not been present previously. Urotropin was at once resumed, and given from the 38th to the 47th day. On the 40th day no bacilli could be cultivated from the urine, and the evidence of cystitis had largely disappeared. The urines of the 42nd and the 47th day showed no bacilli. On the 50th day, three days after stopping urotropin, the bacilli had again reappeared, though in comparatively small numbers. Urotropin was again begun, this time in 20 grain doses three times daily. After 40 grains no bacilli were found. On the 55th day the drug was again stopped. On the 64th day the bacilli had not reappeared.

Case XLIII. Clinical course severe with relapse. Typhoid bacilli present in moderately large numbers on the 14th, 23rd, and 37th days. Urotropin, 10 grains t. i. d., was given from the 38th to the 40th day. Urine of the 40th day, after 40 grains of the drug, showed no bacilli.

Case XLIV. Clinical course moderately severe. Typhoid bacilli first found on 38th day. Urotropin, 10 grains t. i. d., from the 39th to the 43rd day. Urine examined on 43rd, 50th, and 56th day, but no bacilli were found after 40 grains of urotropin had been taken.

Case LV. Clinical course very severe. Typhoid bacilli in moderately large numbers on the 61st and 62nd day. On the 64th day urotropin, 10 grains t. i. d., was begun and continued till the 73rd day. On the 65th day (after 40 grains) the bacilli still persisted in small numbers (hundreds to the cubic centimetre). On the 66th day (after 90 grains) no bacilli could be found. On the 68th day (after 150 grains) a cubic centimetre of urine showed two colonies of typhoid bacilli. On the 70th day (after 210 grains) no bacilli were found. Examinations made upon the 78th, 79th, and 92nd days were similarly negative.

Case LV. Clinical course moderately severe. Urine of 21st and 22nd days showed typhoid bacilli in enormous numbers, as well as a cystitis of moderate severity. Urotropin, 10 grains t. i. d., was given from the 22nd to the 31st day. On the 24th and 27th days no bacilli could be demonstrated. Moreover, the evidences of cystitis had decreased markedly. On the 34th day a few bacilli were found, but they disappeared without treatment on the 35th day. The patient now left the hospital, and was instructed to continue the urotropin as a precautionary measure from the 36th to the 43rd day. Further examination on the 50th day showed no bacilli.

Case LVII. Clinical course extremely severe and complicated by a pneumonia. Death. Bacilli first found in urine obtained at autopsy.

To sum up briefly, we find that—

(1) Of 66 cases of typhoid fever, 14 showed the presence of typhoid bacilli in the urine.

(2) Eleven cases were submitted to treatment with the following results:

(a) Two cases received salol alone, and in one instance the bacilli disappeared.

(b) One case received first salol, with negative results. Urotropin was then substituted for the salol, and the bacilli disappeared almost immediately.

(c) Nine cases (including the case treated first with salol) were treated with urotropin, and in every instance the use of the drug was followed by the disappearance of the bacilli. Moreover, this remarkable result was accomplished in eight out of the nine cases by 60 grains or less of the remedy. A single case (LVIII) required 200 grains to remove the organisms. Seven cases were followed for 7, 9, 13, 14, 17, 19, 43 and 66 days, respectively, after the administration of urotropin was stopped, and no bacilli had reappeared. It is fair to assume, therefore, that in these cases the removal of the typhoid organisms was permanent. One case was not followed subsequent to the omission of the urotropin.

Aside from the question of treatment, few conclusions different from those stated in the previous article can be drawn.

As already pointed out by Horton-Smith, the bacilli are often so numerous as to cause distinct turbidity in the urine. For this reason a turbid urine (freshly passed), especially if acid in reaction, should always be regarded with suspicion. Moreover, if such a urine when examined microscopically, either fresh or stained as recommended by Horton-Smith, shows, as it often does, the presence of bacilli, it can be prophesied with great probability that the organisms are typhoid bacilli, and the results of the cultures can be foretold with considerable certainty.

THE NATURE AND ACTION OF UROTROPIN.

Urotropin was first introduced in 1894 by Nicolaier,* and is said to be formed by the action of four molecules of ammonia upon six molecules of formaldehyde. It appears in the urine partly as urotropin and partly as formaldehyde. Urine containing urotropin gives with bromine water a yellow-brown precipitate of dibrom-urotropin. It appears in the urine as early as fifteen minutes after its administration, and can be demonstrated twelve hours after a single dose of $7\frac{1}{2}$ grains. Indeed in rare instances the drug can be demonstrated for two weeks after its administration has been stopped.

Nicolaier claimed that urotropin would assist in the solution of uric acid concretions, and, further, would prevent the development of bacteria in the urine.

Casper † and Mendelsohn † could not agree with Nicolaier as to the solvent powers of the drug, but as a urinary antiseptic they recommended it very highly, especially in suppurative pyelitis and cystitis. Casper also found urotropin valuable in so-called essential phosphaturia, and before all operations upon the urinary tract he used the drug to render the urine aseptic. Elliott § praises urotropin highly as a remedy in cystitis, and finds it much superior to salol, benzoate of ammonium, resorcin, naphthalin, guaiacol, and boric acid. Elliott observed no ill effects whatever from the use of the drug, and this has been the experience of all other observers. Rarely as the result of large doses there may occur burning sensations at the neck of the bladder, with increased frequency of micturition, but these symptoms disappear immediately upon the omission of the drug or the reduction of its dose.

In my series of typhoid cases a large number had renal disturbance, as evidenced by the presence of albumin and casts in the urine, but in no case did the urotropin increase the gravity of the condition. In one case, as already stated, the drug caused nausea and vomiting, but this effect was due, I am sure, to the fact that, through a mistake,

* *Centralbl. f. d. med. Wiss.*, 1894, p. 897, and *Deutsche med. Woch.*, 1895, p. 541.

† *Deutsche med. Woch.*, 1897, Therap. Beilage, p. 75.

‡ *Berlin. klin. Woch.*, 1898, p. 48.

§ *North American Pract.*, 1897, ix, 451.

the remedy was given on an empty stomach, instead of in the proper manner, after food.

Cohn * reports great improvement in cases of chronic cystitis associated with enlarged prostate and urethral stricture. In cystitis following acute gonorrhœa, and in tubercular cystitis, there was no improvement.

Loebisch † used urotropin in the case of a woman who had large amounts of uric acid in the urine, and who, moreover, had symptoms of stone in the kidney. The use of urotropin was followed by complete recovery.

My own experience with urotropin in conditions other than typhoid fever is limited, but confirms in general the results obtained by others. In a later paper I shall hope to give a detailed account of these cases.

Returning to the question of the urine in typhoid fever, we draw, as the result of these investigations, the following conclusions:

(1) The urine of typhoid patients may contain typhoid bacilli in enormous numbers.

(2) The bacilli may persist in the urine for weeks, months, or even years, and thus constitute (*a*) a danger to the patient himself (cystitis, orchitis, and epididymitis?), and (*b*), what is much more important, a grave source of danger to the public health.

(3) The necessity for the rigid disinfection and supervision of typhoid urine is apparent.

(4) In 9 cases of typhoid fever in which the urine contained typhoid bacilli, urotropin never failed to remove the organisms. In 7 cases the elimination of the bacilli was permanent. In one case the omission of the urotropin was followed upon three separate occasions by the return of the typhoid organisms to the urine. The fourth attempt was successful. One case was not followed after the urotropin was stopped. There is therefore the possibility that in this case also the bacilli returned, but I do not regard this as probable.

(5) In the great majority of cases 60 grains of urotropin are sufficient to remove the typhoid bacilli. Exceptionally, however, as much as 200 to 300 grains are required.

* *Berlin. klin. Woch.*, 1897, p. 914.

† *Wien. klin. Woch.*, 1897, No. 12.

(6) Inasmuch as it is impossible, without bacteriological examination, to tell whether or not a urine contains typhoid bacilli, all typhoid patients should receive urotropin, 30 grains daily for 10 days, beginning with the third or fourth week of the disease, as convalescence approaches. Probably equally good results could be accomplished by the administration of small doses (10 grains daily) of the drug throughout the disease.

I take this opportunity of expressing my thanks to the members of the Visiting and House Staff of the Massachusetts General Hospital for the abundant clinical material placed at my disposal. I am also much indebted to the Director of the Pathological Laboratory, Dr. J. H. Wright, who has assisted me in every possible way in carrying out this work.