

tinin for ten of the remaining thirteen strains of bacteria. These were Culture T, obtained from urine from a patient with pyelonephritis and hemorrhagic cystitis, Culture L, obtained from urine of a patient with pyelonephritis of unknown origin, high temperature and extreme prostration. Culture B, obtained from the vagina of an infant, Culture Lm, obtained from the blood of a prostatic with pyelonephritis, and Culture W, from the blood stream in a case of recurrent pyelonephritis following pregnancy. At the beginning of our work only Cultures T, L and B were used; later the others were added. The vaccine containing these three organisms was administered in three injections of 500, 1,000 and 1,500 millions. The second vaccine containing five strains produced more marked local reaction, and administration was begun at a lower dosage of 150 millions. Inasmuch as some of the cases which were given but three injections, the last three days before operation, developed rise of temperature and pyuria with positive colon cultures late in convalescence, we now continue the inoculations throughout convalescence.

In all the foregoing experiments the mass agglutination test was used. Various dilutions of serum were mixed in equal parts with 24 degree bouillon cultures of the organism, and incubated one hour.

Unfortunately for the rapid progress of these experiments, prostatics with uninfected urine are not common in the wards of the Massachusetts General Hospital. We have studied eight cases, in two of which operation was refused. Table 2 shows the agglutination titer for patients' serum and cultures L and T at entrance and after vaccination.

TABLE 2.—AGGLUTINATION TITER FOR PATIENTS' SERUM AND CULTURES L AND T

Number	Diagnosis	Entrance Strong		After Vaccination Strong	
		L	T	L	T
1	Prostate.....	1: 10	1: 10	1: 500
2	Prostate.....	0	0	1: 250
3	Prostate.....	0	0	1: 350
4	Prostate.....	1: 10	1: 10	1: 20	1: 180
5	Prostate.....	?	1: 10	1: 1,000
6	Prostate.....	1: 2,200
7	Prostate.....	1: 10	1: 60	1: 3,000
8	Prostate.....	1: 120	1: 500

Patients 1 and 4 refused operation. Patient 1 was put on one catheterization a day, and when seen two months later had hazy urine with other bacteria but no colon bacilli. He failed to return for further observation.

Patients 2, 3, 7 and 8 were vaccinated with but three injections, and inoculation was discontinued at operation. The urine remained free from colon bacilli, and there were no symptoms of renal infection until late in convalescence, when all showed colon bacilli and other varieties of bacteria. Patient 3 had definite symptoms of right pyelonephritis and later right pyonephrosis.

Patient 5 showed no rise of temperature during two weeks of preliminary drainage, and passed through suprapubic operation with a rise to 100 F. for two days, followed by normal temperature throughout convalescence. The urine showed a large bacterial flora but no colon bacilli at any time during his convalescence. Five weeks later, ten days after leaving the hospital, he developed a bilateral colon epididymitis

and cloudy urine. *B. coli* was obtained in culture from the urine.

Patient 6 entered the hospital with markedly over-distended bladder and beginning uremia. He was vaccinated with increasing doses of mixed vaccine (five strains), beginning at 150 millions, at intervals of four days, until he was receiving 2,500 million at a time, at which dosage he was kept throughout the eleven weeks he remained in the hospital. He was on constant drainage with inlying catheter for eight weeks. Prostatectomy was done. While his urine showed a slight haze and a few pus cells, it never contained colon bacilli; it is now entirely clear, and culture shows no growth of any variety of organism.

We recognize that our work has not been of sufficient scope to justify conclusions as to the value of colon vaccines as a preventive to colon pyelonephritis, yet our experience leads us to believe that it is more than a possibility. While the colon bacillus is not the only organism concerned in renal and bladder infections, it is the permanent infection, and if avoided the patient is usually able to handle the other bacteria.

It is our belief that the immunity conferred by colon vaccine is of short duration, probably not exceeding three or four weeks.

The administration of vaccine in prostatics should be made to extend over the period of convalescence.

87 Marlborough Street.

PYELITIS IN CHILDREN*

WILLIAM C. QUINBY, M.D.

BALTIMORE

The present knowledge on the subject of pyelitis, or pyelocystitis, of infancy and childhood is well reviewed in an article by R. M. Smith¹ of Boston published last year. Since this, the subject has also been dealt with in the papers of Kowitz,² Wood³ and Fischl.⁴

As is well known, by far the commonest type of pyelitis in children is that due to bacilli of the colon-aerogenes group. The clinical picture caused by such infection of the urinary tract is clear cut, recognized generally, and will not be discussed in this place. On two aspects, however, a review of the opinions of writers shows that there exists marked lack of unanimity: the first is in regard to the method of causation of the infection; the second embraces the question of treatment. It is in regard to these points that I wish to call attention.

MODE OF INFECTION

The three methods by which the infecting organisms may reach the renal pelvis are by direct extension upward from the lower urinary passages, by the general blood stream, and by way of the lymphatics. The first method, that of upward extension, has for long held the field as the most probable and the most

* From the J. B. Brady Urological Institute, Johns Hopkins Hospital.

¹ Read before the Section on Genito-Urinary Diseases at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

² Smith, R. M.: Literature of 1913 and 1914 of Infections of the Genito-Urinary Tract in Children, *Am. Jour. Dis. Child.*, April, 1915, p. 338.

³ Kowitz: Ueber bakterielle Erkrankungen der Harnorgane im Säuglingsalter, *Jahrb. f. Kinderh.*, 1915, **82**, 309; *München. med. Wchnschr.*, June 16, 1914, p. 1341.

⁴ Wood: Acute Pyelitis: A Cause of Obscure Fever in Infancy, *Arch. Pediat.*, 1915, **32**, 199.

⁵ Fischl: Erfahrungen über Zystitis im Kindesalter, *Prag. med. Wchnschr.*, 1915, **40**, 163.

common. Lately, however, this has been disputed, and several writers, Kowitz and Wood in particular, are of the opinion that the bacteria reach their location by way of lymphatic channels leading from the intestine directly to the kidney, or by the blood stream. The reasons for this change of feeling are, among others, that the ascending route has never yet been clearly proved, and cases are found not infrequently in which no involvement of the lower passages can be demonstrated. The same arguments here as to mode of ingress of the bacteria are in no way confined to children, but apply to adults as well. Kowitz goes so far as to assert that the infection is almost never an ascending one, but a direct result of previous intestinal involvement. He prints a most suggestive incidence curve showing that the majority of his cases occurred during the months from July to November: months during which intestinal diseases are most common in children.

It would seem that the theory of ascending infection has been losing ground of late, and it is probable that the frequency of this mode of ingress has been exaggerated in the past. There still remains, however, the well known fact of the large preponderance of girls afflicted over boys. Adherents of the ascending infection theory have always explained this by the closer proximity of the female bladder to the exterior, with resulting increased chances of infection of the child's vulva from the anus. On those who deny this mode of origin rests the burden of offering some other plausible explanation for this undoubtedly more frequent infection of girls. None has yet been suggested.

Thomson,⁵ who has written two excellent papers on this subject, says on this point:

The great preponderance of female patients seems . . . to force us to the conclusion that ascending infection by way of the urethra must be a common occurrence; and the excess of girls over boys probably represents the frequency with which urethral infection takes place. It seems very unlikely that the colon bacilli can find their way up the lumen of the male urethra. The greater prevalence of antecedent diarrhea in boys would probably cease to exist if we were able to subtract from the list of girls the primary cases infected per urethram.

He in no way denies the occurrence of cases in which the infection has had origin in the intestines and been carried thence by the blood or lymph.

PROGNOSIS AND DURATION OF THE DISEASE

Of the sixty cases collected by Jeffreys,⁶ all but six were due to the colon bacillus. Fifty-three were in females, seven in males. Only twenty-one of the sixty were cured. Nine patients died: six of the urinary trouble, and three of some other disease. Six were unrelieved. Twenty-three were improved, that is, were without symptoms, but still showing pus in the urine. Kowitz gives the details of forty cases, of which fifteen patients died. Langstein,⁷ on the other hand, considers that 90 per cent. of the patients recover. It is quite evident, therefore, that the actual mortality is rarely an insignificant one, and in certain localities may run as high as 37 per cent. (Kowitz). But besides this, the morbidity of the disease is con-

siderable, some cases existing for three years or more, and ending either in recovery or with some definite nephropathy as a result of the chronic infection. Marsh⁷ says that the prognosis of the disease is favorable, "but before pronouncing the patient cured the urine should not only show an absence of organisms and of pus cells, but should also be culturally free. . . . In spite of all treatment many cases become chronic; in these acute exacerbations alternate with long periods of quiescence, but the urine never becomes entirely free from pus cells and organisms."

TREATMENT

Smith says:

The one form of treatment against which no dissenting voice is raised is the administration of large quantities of fluid. Further than this there is apparently no specific treatment. In many of the acute cases the patients get well untreated.

The English school of pediatricians advocates the so-called "alkaline" form of treatment, in which the urine is kept alkaline by the administration of potassium citrate. Others prefer to make the urine acid by giving sodium benzoate, while still others advise changing frequently the reaction of the urine by the alternate administration of these drugs. Some writers are warm advocates of hexamethylenamin; others advise salol. The use of vaccines has everywhere encountered disappointing results. But the majority opinion seems to favor the use of alkalies.

COMMENT

Such discrepancies in the clinical course of the disease, with their resulting differences of opinion as to its proper treatment, seem to me to be explained by what we know of the protean characteristics of the bacteria of the colon group. The colon bacillus, *paracolon bacillus* and *Bacillus lactis-aerogenes* form only the general divisions of a group of organisms showing many and often wide variations in their virulence and resistance to destructive agents. It is clear, therefore, that while in one case the administration of potassium citrate may set up conditions inimical to further growth of the infection, and thus bring about a cure, in another case such "alkaline" treatment may be entirely without avail, though here acid-producing drugs may succeed. In every case, therefore, we are logically driven to the careful examination of the biologic characteristics of the individual organism by which the patient is infected.

In this regard the recent work of Clark⁸ is not only of great interest, but bids fair to go far in overcoming some of the uncertainties noted above. Together with his co-worker Lubs, he has made a large number of observations on bacteria of the colon-aerogenes family with regard to their power of gas production and also of acid production. The degrees of acidity or of alkalinity compatible with continued cultural life of the organism were measured by determining the hydrogen ion concentration of cultures at frequent periods of their growth. By these means there can be differentiated two groups of organisms, called, according to their ability to produce gas from fermentation of carbohydrates, "high" and "low ratio" cultures. Further investigation has shown that the gas

5. Thomson: On Acute Pyelitis Due to *Bacillus Coli* as it Occurs in Infancy, *Quart. Jour. Med.*, 1909-1910, 3, 251; Infection of the Urinary Tract in Children by the Colon Bacillus, *Lancet*, London, 1913, 2, 467.

6. Jeffreys: Infection of the Urinary Tract in Children by Coliform Organisms, *Quart. Jour. Med.*, 1910-1911, 4, 267.

7. Quoted by Smith (Footnote 1).

8. Clark: The "Reaction" of Bacteriologic Culture Media, *Jour. Infect. Dis.*, 1915, 17, 109. Clark and Lubs: The Differentiation of Bacteria of the Colon-Aerogenes Family by the Use of Indicators, *ibid.*, 1915, 17, 160. Clark: The Final Hydrogen Ion Concentrations of Cultures of *Bacillus Coli*, *Jour. Biol. Chem.*, 1915, 22, 87.

ratios of such cultures correlate perfectly with the differences in the metabolism of different species as shown by their acid production, that is, their hydrogen ion concentration. And so, by using indicators to determine the hydrogen ion concentration as developed by Sörenson,⁹ instead of the more complicated electrical method, we have a simple diagnostic test which will accurately determine to which of two groups, at least, the organism under consideration belongs.

With this knowledge at hand, it should be our endeavor to regulate the reaction of the urine, either by the administration of citrate or benzoate as the case may be, so that it will be as far as possible outside the range of hydrogen ion concentration exhibited by the infecting organism. Cultures from the urine should be grown on the special mediums used by Clark and Lubs⁸ from which the range of acid production can be determined. Similar observations should then be made on the urine. Comparison of these two factors will then determine in which direction the reaction of the urine should be adjusted so as to create conditions least favorable to the organism. By this means we shall be doing our utmost on a physicochemical basis to combat the continued existence of the bacteria.

Though sufficient evidence is not yet at hand to lead to a definite decision in the matter, it is my belief that the foregoing form of treatment, based on an accurate knowledge of the biologic characteristics of the infecting organism, will be followed by an increased number of complete cures. It is probably not to be expected, however, that we shall thus be able to control every case; some will still be found in a chronically infected condition, symptomless, but none the less diseased. I would strongly advocate for such chronic cases injection into the kidney pelvis of silver nitrate solution of a strength sufficient to cause a moderately sharp reaction, say from 0.5 to 1 per cent. The marked and often surprisingly quick benefit of such treatment in cases of pyelitis in adults is familiar knowledge to all present day urologists. Heretofore such treatment has not been applied to the child bearing the same type of infection. This is due to the fact that the family physician or pediatrician has felt that such instrumentation is impossible because of the small size of the urethra. In the female, however, with the exception of very young babies, the urethra is dilatable to a size to admit a No. 16 or 18 F. instrument, and cystoscopes of this size carrying a single catheter are easily constructed and handled. It will be found easier in most cases, however, to use direct catheterization through an open cystoscope, with air distention of the bladder. A general anesthetic is necessary, but this need rarely be prolonged over fifteen or twenty minutes at the most.

Though ureteral catheterization is not especially difficult in the female child, it is quite impossible through the normal urethra of the male, and in this respect it is fortunate that the disease incidence noted above shows male children to be in marked minority. It is possible, however, to reach the ureters in the male child by a median perineal section, through which, after dilation of the bladder sphincter, a small cystoscope can be passed. Though cases in which such radical treatment as this is justifiable will naturally be very infrequent, it is quite evident, nevertheless, that such operation with its temporary inconveniences is

preferable to a condition of long persisting infection leading to permanently damaged kidneys.

CONCLUSIONS

It is to be noted that pyelitis in children is more often a serious or even fatal malady than has been thought in the past. Though female children are attacked more often than male, this difference is not so great as was held by the earlier writers. The origin of the disease seems quite surely to be from the intestinal tract in a good many cases, but the theory of infection ascending from the lower urinary tract cannot yet be entirely disproved. Medical treatment has been too haphazard heretofore. It should be based on the accurate knowledge gained by estimation of the properties of the specific infecting organism. This can be obtained by determining the hydrogen ion concentration of cultures both of the organism and of the urine. Pediatricians and internists have not yet appreciated the value and possibilities of pelvic injections. Wherever possible this should be urged in those cases in which the urinary tract does not become entirely free from infection within a reasonable time.

My two main objects in calling attention to this subject are to advocate a treatment based on the use of the newer and more accurate methods of bacteriology, and to remind our colleagues the pediatricians that for those few cases which resist this treatment, the urologist can often place at his command a method of local treatment which holds high hopes of success.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. CRABTREE AND CABOT, AND QUINBY

DR. IRVIN S. KOLL, Chicago: Dr. Crabtree verifies the findings before this section two years ago. There is only one difference, and that is his finding the bacteria in the tissues. I have been unable to isolate from the urine after twenty-four hours any of the colon bacilli after having produced an infection in the kidney, and have also been unable to get on staining any bacteria in the pelvis after twenty-four hours in those cases where I was particularly careful not to traumatize the kidney. As Dr. Crabtree also stated, I have been unable to get any of the colon bacilli in the parenchyma. I have seen a number of cases of pyelitis in pregnant women. I prefer the title "pyelitis during pregnancy," rather than "pyelitis of pregnancy." An intelligent patient who knows something of the diseases of her childhood will, in 90 per cent. of cases, tell you that she had some kidney trouble, probably a cystopyelitis, in early childhood. What does this mean? It means that all of these years she has had bacteria in the urine without any symptomatic manifestation. Possibly a microscopic examination of the urine would fail to show any pus cells, but a bacteriologic examination of the urine will show bacteria. This leads up to the point I attempted to bring out several years ago in my study of the colon infections of the kidney, namely, that a patient with pyelitis, or pyelonephritis, as I prefer to call it, should never be pronounced cured until repeated cultures taken from the urine through the ureteral catheter fail to show bacteria. As to specific therapy, I wonder if any one has made sections of a kidney in an animal following the injection of 0.5 or 1 per cent. silver nitrate to see just exactly what it does. I have not. But you know what the effect of silver nitrate is on any mucous membrane; it is distinctly corrosive, and it forms a sort of membrane over the surface. We know that the bacteria are beneath the surface, and while there is a sharp reaction, is it a beneficial one? I wonder if we do not get a great deal of destruction? I still am using the solution of aluminum acetate with the same good results that I got three or four years ago; 0.5 to 2 per cent. aluminum acetate injected into the pelvis of the kidney until you fail to get the bacteria in the urine will give good results which will be permanent.

⁹ Sörenson: *Compt. rend. trav. de Lab. Carlsberg*, 1909, 8, cited by Clark and Lubs (Footnote 8).

DR. HENRY F. HELMHOLZ, Chicago: I was very much interested in what Dr. Quinby had to say about the pyelitis of infancy, and have been interested in the subject from very nearly the same point of view that he has, namely, determining the acidity or alkalinity in which the colon bacillus will grow. The point he made of titrating or determining the hydrogen concentration of the culture medium after the organism is grown is not what we are after, but to get a medium in which the organism will not grow. In a series of about twenty cases we have grown the organism isolated in broth of varying degrees of alkalinity and acidity, and in nineteen cases the range was from 2 per cent. bacteriologic acidity to 2 per cent. bacteriologic alkalinity. Only one of these organisms grew beyond that range.

DR. WILLIAM F. BRAASCH, Rochester, Minn.: In regard to the prognosis of these cases of pyelitis of infancy, my observation has been that rarely is it true that a case of chronic pyelonephritis as seen in the adult gives a history of having had any infection or ordinary trouble in infancy or childhood. I realize the fact that cases of pyelitis may occur in infancy without urinary symptoms. It is not the rule, however. So there must be a distinct difference between the pyelitis of infancy and that of the adult, because the adult rarely gets well. By treatment we can improve the condition, but it is exceptional for a patient to recover entirely, at least on cultural examination.

DR. GRANVILLE MACGOWAN, Los Angeles: I cannot agree entirely with Dr. Braasch. There are patients with pyelonephritis who get well if properly and persistently treated. I have used Dr. Koll's method but I do not think as favorably of it as I do of the use of silver nitrate, as recommended by Dr. Geraghty. Many get so well that cultures made from the urine do not show any colon bacilli, and I have seen many women with pyelitis during pregnancy giving an intermittent history of pyelitis or pyelonephritis from childhood.

DR. EDWIN BEER, New York: I would like to ask Dr. Crabtree on what he bases his conclusion that after inoculation with these colon vaccines he is really getting the benefit that he seems to think he is getting, because as I reflect on my own experience I do not find that I am troubled with repeated attacks of pyelonephritis, either after the first stage of the operation or after the prostatectomy, and it is just possible that in the Boston clinic they are getting different results now which may not be attributable to the preliminary vaccine treatment. I believe that if everybody will talk, we will probably find that there are more people who fail to see these postoperative pyelonephritides than Dr. Crabtree's report suggests. The greatest difficulty in this field to me has always been the diagnosis. In an acute case of pyelonephritis—or pyelitis, as the pediatricists call it—it is very difficult to decide as to the extent of the pathologic lesion. Is it a pyelitis *per se*, or is the kidney involved also? Is our patient suffering from pus foci in the parenchyma? In the acute cases I believe it is almost impossible to differentiate immediately. You will hear that the functional tests will show a marked diminution in excretion if the parenchyma is involved, but I am not sure that that is absolutely reliable. Later in the subacute or chronic stages the recognition of parenchyma involvement is simpler. I suppose one has followed the method I published eight years ago. I would like to add a note to that publication in which I called attention to the fact that methylene blue is stored in the minute parenchyma abscess and is later discharged bound to the pus, as these abscesses discharge into the pelvis of the kidney. During the last four or five years I have encountered the same phenomenon with indigocarmin.

DR. E. G. CRABTREE, Boston: In carefully followed functional tests with phenolsulphonophthalein we have noted that following decompression of kidneys which have been the seat of back pressure there is uniformly a fall in output which we attribute to congestion. It is of only a day to three or four days' duration. If the case does not become infected, the phenolsulphonophthalein output continues to rise until at the end of a week or ten days it has reached a safe, stable, operable level. However, the intervention of a pyelonephritis at any stage of the game suddenly drops the functional test down, in some cases with a previously 45 to 50 per cent. output to

less than 5 per cent. The cases so infected show, as I have tried to indicate in my paper, a definite increase in agglutinating power of their serum for their colon bacillus. The patients we have vaccinated previous to operation have shown this same increased agglutinating power. They have, as a rule, run without postoperative temperature elevation, save for 99 to 100 degrees for the first two days, which is unusual following suprapubic prostatectomy. The urine in these cases has uniformly shown infection after operation with bacteria other than the colon bacillus. In some of our cases, in which we did not continue the use of vaccine throughout convalescence, the patient developed pyelonephritis or epididymitis late in convalescence, which leads us to believe that the protection afforded by colon vaccine is of short duration, three to four weeks at most.

DR. WILLIAM C. QUINBY, Baltimore: In regard to the question asked by Dr. Koll as to whether any experimental observations have been made on the injection of silver nitrate, none have been made by me because I did not think it necessary. Silver nitrate cures the patients, and that is the main point in the matter. From a histologic point of view we know that silver nitrate does cause desquamation which has been preceded by round cell infiltration and vascular congestion which the pathologist would probably call inflammation. It is during this process of reaction that the bacteria have been shown to disappear. In regard to the remarks of Dr. Helmholtz, probably I did not make myself clear. I was very much interested in his remarks because they bring up the thing that I am asking you to avoid; namely not to speak of "acidity" or "alkalinity" in percentages, or in some term that you must qualify, but to use a term by which the physician or scientist will know what you are talking about. In other words "2 per cent. alkalinity" or "2 per cent. acidity" does not mean anything definite unless the details of the method by which such was determined are first explained. If you state this degree of acidity or alkalinity in terms of hydrogen ions it is analogous to saying that a patient has a temperature of 101 degrees; no qualification is necessary, and every one knows what is meant. We ought to stop this loose writing and talking. We see many statements in the literature that a patient's urine was "very acid." That does not mean anything. Let us state it as a perfectly definite degree of concentration of hydrogen ions, something which we could not do ten years ago. I was very much interested in the point brought out by Dr. Beer about the methylene blue being retained and subsequently staining. I have not had his experience with methylene blue, but I have had experience with indigocarmin.

A NEW METHOD OF ACIDOSIS THERAPY

BLOOD TRANSFUSION FROM AN ALKALINIZED DONOR, WITH REPORT OF CASE *

ALEXANDER O. GETTLER, PH.D.

Pathologic Chemist, Bellevue Hospital; Assistant Professor of Chemistry, University and Bellevue Hospital Medical College

AND

EDWARD LINDEMAN, M.D.

NEW YORK

It is generally believed that the alkalinity of the blood of a normal person is fairly constant and unalterable.¹ Our purpose is to show that the alkalinity of the blood of a normal person can be greatly increased by a very simple procedure, and furthermore, to point out the feasibility of such alkalization of the blood of a normal donor to enhance its therapeutic value in blood transfusion for the treatment of acidosis.

Briefly stated, when the alkalinity of the blood is diminished through excessive acid products formed

* From the Department of Pathology, Bellevue and Allied Hospitals.
1. A. W. Sellards (Bull. Johns Hopkins Hosp., 1912, 23, 289) has shown that the tolerance to alkali is higher in acidosis than in normal individuals as measured by the urine. No blood examination or blood studies were made.