

that crude opium in addition to the various isoquinolin derivatives also contains various inert bodies such as gums and the resins, etc., it is clear that it is even more constipating than a combination of the pure total alkaloids alone.

Thus, as a result of careful pharmacological investigations, it is evident that morphin and opium possess very different therapeutie values in respect to their effect on the intestinal movements.

ACTION ON THE PYLORIC SPHINCTER. It may be well to devote a paragraph to the action of some opium alkaloids, and especially of papaverin, on the pyloric valve or sphincter, in view of their possible therapeutic applications. The spasmodic effect of morphin has already been sufficiently described. The effect of papaverin on the pyloric sphincter is a diametrically opposite one. Roentgen-ray studies have shown that papaverin produces relaxation of the pylorus. The same has been confirmed by the present author in experiments on the isolated pyloric ring (Fig. 6) and the ileocecal sphincter (Fig. 7). Holzknecht and Sgulitzer²² have suggested injections of papaverin in differential diagnosis of functional and organic spasm of the pylorus. Again, Delprat²³ injects papaverin for the relief of pylorospasm in infants. In connection with a study of the effects of papaverin on the ureter and other smooth-muscle tissues *in vitro* it occurred to the author to suggest its use by mouth in infantile spasm of the pylorus. Inasmuch as the toxicity of papaverin is very low, such a procedure was deemed not to be dangerous. Accordingly, solutions of papaverin-hydrochloride have been administered to infants with pylorospasm in a few cases through a stomach-tube with very encouraging results.

RENAL INFECTION.¹

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At the outset we confess to have accomplished nothing more important than the reduction to something like a satisfactory working basis of our sometime inapt conception of this subject.

In common with many others, we have been depressed by the enormous extent and wondrous complexity of the literature to which we are now perhaps contributing a further burden. However, a careful compilation and consultation of our own experience, taken

²² München. med. Wchnschr., 1913, iii.

²³ Nederl. Tijdschr. v. Geneesk., 1915, ii; 1311.

¹ Read before the Tri-State Medical Society of Virginia and the Carolinas at Durham, N. C., February 21-22, 1917.

in conjunction with a review of certain selected portions of this literature, have gradually evolved conclusions of some definiteness which it may be worth while recording briefly. In a series of 125 cases subjected to cystoscopic diagnosis during the past two years about 30, or 24 per cent., were found to have extrarenal causes for the urinary symptoms presenting, and these, of course, are immediately excluded from the present consideration. Of the remainder, 60, or 63 per cent. of the true urinary group, were cases of renal infection of the non-tuberculous type. To this number are added, for general consideration, about 20 other cases in which the presence of renal infection was so evident as not to require cystoscopic diagnosis, and in which, for one reason or another, it was found inadvisable or impossible to employ the accepted methods of cystoscopic treatment. Thus, in a grand total of 115 urinary cases constituting the basis of this report, 80 were cases of non-tuberculous renal infection, presenting an incidence of nearly 70 per cent.

GENERAL CONSIDERATION. It would appear that the chief cause of the disastrous confusion pervading the literature lies in two errors: (1) The attempt to erect into distinct clinical and pathological entities, conditions which are most probably consecutive events in the same general process. (2) The assumption that the character of the organism involved has no determining influence upon the course pursued by this general process in a given instance.

Certainly, the picture has unfolded with greater clarity for us, and we have been able more intelligently to estimate our own cases since we have come to realize: (1) that the commonly accepted differentiations (pyelitis, pyelonephritis, pyonephrosis, perinephritic abscess, etc.) in reality represent initial, concurrent, or terminal stages of a general process (renal infection); (2) that the nature of the involved organism as between the pyogenic cocci on the one side and the ubiquitous colon bacillus on the other has a profound influence upon pathology, symptomatology, and treatment.

In reference to the former there has been a gradual swing of sentiment in this direction in the last few years; as to the latter, it has been extremely interesting to note, running through the recent literature, a skein representing a true conception of the situation by a very few, and, by a few others, a clinical and therapeutic differentiation with an apparent lack of understanding of the pathological basis therefor. Most recently of all, Cabot and Crabtree² have presented a report which, though of no striking originality, is, in our judgment, of monumental importance in that it gathers into a coherent whole the scattered threads of this skein and surrounds it with a framework of case summaries representing investigative work of a very high order.

Briefly stated, this new conception of kidney infection assumes,

² Surg., Gynec. and Obst., November, 1916.

on what appears to be sufficient evidence, that in the ordinary case the involvement begins primarily in the substance of the organ, including the pelvis and perinephritic tissue secondarily, if at all, so that a simple pyelitis rarely, if ever, exists without at some stage an inclusion of the parenchyma, though the same cannot be said of perinephritic abscess, which may at times be of entirely extra-urinary origin. The bacteriology concerns essentially the pyogenic coccus group on the one side and the typhoid colon group on the other. In the first named the process is more or less limited to the kidney itself, involving the pelvis little if at all; the lesions here are cortical abscesses, septic infarcts, diffuse suppuration, capsulitis, capsular abscess, and perinephritic abscess. In the typhoid colon group, on the contrary, the tendency is distinctly toward an attack on the convoluted tubules and the pelvis, and the lesion is a pyelonephritis which in some cases is so predominantly associated with the pelvis as to amount in clinical significance, if not in pathological accuracy, to a "pyelitis" pure and simple. The essential point in the entire consideration is the fact that the coccus has a strong inclination to abscess production and the colon bacillus none at all, though a pyonephrosis may easily (and necessarily) result from a bacillary infection if a ureteral obstruction becomes at any time added to the picture.

Etiology. Considering the etiology, we are compelled by our experience to discard, at least in part, the time-honored generality that renal infection is dependent upon an antecedent focus of infection and a kidney whose resistance has been lowered by such predisposing factors as stone, traumatism, obstruction, new growth, mobility, etc. The necessity of a bacterium is, of course, evident and the germ unquestionably comes from a preëxisting focus elsewhere in the body. This focus may be a tooth, a tonsil, a furuncle, the gall-bladder, the appendix, the intestine at large, etc.; in the majority of instances we can merely assume its existence without being able to determine its location.

The other half of the generality does not hold up so well.

In determining the occurrence of infection, predisposing factors of the types noted are of very great importance when they are present, but in a very high proportion of cases they are entirely absent. In our series this factor entered into the situation in only 35 per cent. of cases. In the others the nature of the predisposing element was as obscure as the identity of the antecedent focus. Very probably the common determining factors are less often the gross lesions enumerated above and more often the impalpable influences associated with lowered systemic resistance in general, chronic toxemias (particularly from the intestinal tract), the virulence of the particular strain of germ involved, the number of organisms reaching the kidney, and the duration of their travel kidneyward.

In this connection we call attention to several important considerations. The kidney is an excretory organ for bacteria comparable to the liver. Germs are probably being constantly fed into the blood stream from various sources and carried to these organs for elimination. It is possible for this elimination to occur without any damage to the kidney itself. We have recovered pure cultures of pneumococci from the urine of a pneumonia patient who had no renal involvement. Numerous other such cases have been reported. Rosenow has shown, however, that germs lurking in infected areas may from time to time undergo modification and acquire hitherto unpossessed selective affinities for certain structures including the kidney. Such a germ feeding into the blood stream would no longer harmlessly pass the kidney. On the contrary, it would here find its new elective localization and fall upon it. Thus, so far as organisms are concerned, they may be immediately of such high virulence as to infect the kidney promptly; they may be of a lower grade of virulence, but in such massive number as to have essentially the same effect: they may be of such a type as to fall an easy prey to the physiological activity of the kidney and do no harm; or, finally, they may originally have been of this latter class, but subsequently have developed selective destructive powers against the kidney. The germs with which we have dealt in our series are in 54 per cent. of the bacteriologically differentiated cases colon bacilli and in 30 per cent. staphylococci and streptococci. There were 16 per cent. of mixed infections, and evidence in many indicating that the colon bacillus was a secondary offender. In reference to the predisposing resistance—lowering factors, the outstanding feature, apart from the minority of gross lesions already mentioned, was chronic constipation, which with its accompanying toxemia was present in such a high percentage of cases as to demand very serious consideration. In quite a large number of cases no predisposing factor whatsoever was evident.

As to the avenue traveled by the organism in its journey to the kidney, the discussion is already voluminous enough and heated enough to make it unnecessary for us to add another word to it. We content ourselves therefore with the bare assertion that we consider the evidence:

1. Overwhelmingly against the so-called ascending infection except in a very few cases.

2. Not sufficient to identify the infection with the lymph current as a common occurrence.

3. Conclusively in support of a hematogenous route in a vast preponderance of cases.

SYMPTOMATOLOGY. Pyonephrosis is a terminal event with a symptomatology of its own which need not be considered at this time, and much the same may be said of the perinephritic abscess consecutive upon primary renal conditions. Of the latter the infec-

tions may vary from the extremely chronic to the violently acute. From the prognostic and therapeutic view-point a bacterial differentiation of the acute forms is important, and is often possible when all available diagnostic measures are employed. A coccus infection of severe grade will present high fever, chills, rapid pulse, high leukocytosis, pain on the affected side, abdominal tenderness and spasm, and a rapidly progressive toxemia. Blood cultures may show the organism. A colon infection of severe grade will present the same symptoms, though usually in lesser degree, and commonly the toxemia will not be so marked. Here also a blood culture will often prove positive. For immediate diagnostic purposes, however, consideration of the urine and function will prove of greatest value. Involving a portion of the kidney distant from the pelvis, and not particularly concerned in the elimination of phenolphthalein, a coccus infection often produces little or no change in the microscopic appearance of the urine or of the functional capacity of the kidney as measured by the dye output. So much is this true that the pronounced abdominal symptoms and the insignificant urinary findings often lure the diagnostician into an ineffective intraperitoneal operation. With bacillary infections, on the contrary, the pelvis and the convoluted tubules are primarily involved, pus, bacteria, and other pathological elements appear promptly in the urine, and the function is very profoundly affected.

The question of whether any renal infection is ever strictly unilateral is still *sub judice*. We believe the vast majority of such infections, acute and chronic, to be bilateral in spite of temporary absence of pus and bacteria from one of the kidneys. Notwithstanding this we feel convinced that there is definitely, though rarely, such a condition as an acute unilateral infection of the type described by advocates of this belief as "suppurative infarct." Furthermore, we believe that in the common bilateral acute infections the pathology is often, if not commonly, much more pronounced upon one side than the other.

We pass over the mixed infections representing the engrafting of a secondary colon infection on a primary coccus base or the reverse. Such cases, particularly when associated with gross lesions such as stone or stricture, present a complex urinary picture and a pathology still more complex. In most instances the interpretation of the picture is a matter of mere conjecture.

In the symptoms summary which follows, based on the cystoscopic series, we include both the chronic and the ordinary acute cases, excepting only the fulminating types just described. Certain cases appear to have been chronic from the outset; the usual history is an original more or less acute attack, subsidence into a mild chronic condition (often with almost complete remissions), and thereafter periodic acute or subacute outbursts. The chief characteristics noted are as follows:

Age, Sex and Race. We have wasted no time over these considerations. Renal infection is no respecter of person, and occurs frequently in young and old, male and female, white and black.

Etiology. Apart from the gross accompanying lesions referred to more in detail under the head of associated conditions the etiology is often quite obscure. In 30 per cent. of our cases it was entirely undetermined, and in many others it could only be assumed. Of these latter a group constituting nearly 20 per cent. of the whole presented chronic constipation as the outstanding factor. A recent history of typhoid fever was present in 2 cases. Definite pre-existing foci were determined in 10 per cent. of cases as follows: Pyorrhea, throat infection, puerperal sepsis, operative wound infection, salpingitis, and traumatic hand infection. Reduplication of ureters was present in 3 cases, stricture of ureter in 5 cases, great mobility of kidneys in 5 cases, stone in 8 cases.

Bacteriology. The offending organism was identified in slightly over 50 per cent. of the cases. In 5 per cent. no germ could be located either by stain or culture. In the remainder the bacteriological records are incomplete, a gross error which in the future we shall attempt to avoid. Of the cases in which the germ was identified, 54 per cent. were colon infections, 30 per cent. coccus infections, and 16 per cent. mixed colon and coccus infections.

Course. The clinical duration of the lesion varied between one day and fourteen years.

Associated Conditions. In 35 per cent. of cases gross predisposing urinary lesions such as stone, stricture, and prolapse were present. In the stone cases it was often difficult or impossible to judge between cause and effect, and the same may be said of the strictures. So far as prolapse is concerned, it is interesting to note that in all cases the mobility was unilateral, but the infection bilateral except in one instance. A great variety of extra-urinary associated conditions presented themselves, mostly negligible from the etiological point of view. Pelvic complications in women were found rather often, particularly salpingitis, displacements of the uterus, and large fibroid tumors. The previous histories of the patients contained the usual citation of childhood infections, of which no particular note is taken here. Considerable significance attaches to the frequency with which these previous histories contained reference to "malaria," chronic appendicitis, and gall-stones. In several of these, long treatment, removal of the appendix, or exploration of the gall-bladder had failed to do what the ureteral catheter subsequently easily accomplished.

Side Affected. In 70 per cent. of cases the infection was bilateral. The unilateral cases were either of the type known as "infaret" or presented some condition definitely interfering with the vitality of the kidney involved: solitary kidney, rudimentary third pelvis, strictured ureter, stone in pelvis or ureter, mobility with kink of

ureter. We are inclined to question the existence of a unilateral infection exclusive of these two types. No such case appeared in our series. It is important to note, however, that the infection is commonly predominant upon one side, and that its existence upon the other (where it may be entirely dormant) can often be demonstrated only after very careful microscopic and cultural examination.

Initial Symptom. This was definitely stated in 90 per cent. of cases as follows: pain, 46 per cent.; bladder disturbance, 32 per cent.; fever, 6 per cent.; vomiting, 4 per cent.; general weakness, 2 per cent.

Predominant Symptom. In about 88 per cent. it was possible to determine the predominating symptom of the attack. In a few cases two or more symptoms were given equal prominence, and this accounts for the apparent discrepancy in the percentages: pain, 60 per cent.; bladder disturbance, 15 per cent.; fever, 10 per cent.; malaise, 10 per cent.; vomiting, 2 per cent.

Bladder Disturbance. Frequency of urination was present in 81 per cent. of cases and painful urination in 66 per cent. Combining the two a total of 86 per cent. of cases presented bladder disturbance of some kind and degree, occasionally slight but usually quite marked.

Pain. In our cases this presented a definitely higher incidence than that observed by many others, and it is in fact one of the outstanding features of the symptomatology. It was present in 77 per cent. of cases, and varied from a dull ache to a seizure of such severity as to require morphine. The pain was commonly located in the lumbar region, but sometimes appeared over the bladder, throughout the entire abdomen, under the costal arches, in the inguinal regions, and across the sacrum. It is interesting to note that it was commonly unilateral in spite of the fact that in many cases the urine of the opposite side showed findings of equal, sometimes greater, significance. The same thing may be said of local tenderness, which was found in 60 per cent. of cases.

Fever and Chills. A definite history was obtained in 54 per cent. of cases.

Gastro-intestinal Disturbances. Gastro-intestinal disturbances were present in 43 per cent. of cases.

Malaise. This was noted in 40 per cent.; in about 25 per cent. definite loss of weight was complained of.

Pyuria. This was absent in but 1 case, a perinephritic infection apparently originating in a kidney lesion without pelvic outlet. The amount of pus present varied enormously and offered no constant indication of the gravity of the process. Some of the most stubborn of the cases showed but small amounts. The findings were bilateral except as noted under "side affected," but commonly there was considerable difference in the two sides. We observed with interest that many cases which at first appeared unilateral eventually developed pus and positive cultures on the other side.

Hematuria. Blood was present in the urine in sufficient quantity to be seen by the patient in 10 per cent. of cases. No attempt was made to compile the microscopic findings.

Leukocytosis. In the more acute stages there may be leukocytosis of varying degree. Septic infarcts commonly produce a high total leukocyte and polynuclear count. In the chronic cases it is distinctly unusual to find any blood reaction. Furthermore, it is important to note that in a certain percentage of acute cases there will be no blood change. We have witnessed an initial attack with chills, malaise, temperature of 103°, and a normal leukocyte and differential count.

Function. In something over one-third of the cases separate function test was done with phenolphthalein as an indicator. In common with the experience of others our results here have been somewhat confusing, and we are more and more impressed with the importance of a careful consideration of the clinical aspects of the case before placing too great a reliance upon the dye tests in the chronic cases. In several instances the pathological condition has been accurately pictured by the indicator, a low or absent reading suggesting the nephrectomy subsequently done, with a classical compensation on the opposite side. At other times, however, very low readings have meant nothing more than the presence of a stone or some other disturbing element which did not essentially involve the parenchyma, and the removal of which would permit prompt return of the function to normal. As it is often impossible to separate these two types clinically, direct inspection of the interior of the kidney at the time of operation is the only safe guide to nephrectomy. In a very few cases we have found higher function on the affected side than on the other (one septic infarct and one stone kidney). However, certain modifying elements were present in both these cases. Finally, we have encountered several cases of apparent hyper-permeability to the dye in which abnormally high readings were present in spite of more or less marked lesions on one or both sides.

Cystoscopic. In 40 per cent. of cases the bladder picture was absolutely negative, and in 23 per cent. nothing further was noted than an edema or congestion of the trigone suggesting a chronic irritation. Cystitis was well marked in 20 per cent. of cases and of moderate severity in 12 per cent. of others. One cannot fail to be impressed with the remarkable ability of the bladder to resist infection in the presence of a stream of purulent and bacteria-laden urine which may have been flowing across it for years. In slightly over 40 per cent. of cases, pyelography was done with collargol or thorium, and with no bad results. This measure was of considerable value, but we could not so systematically as Braasch (though quite frequently) trace in the pelvic outline the signs of infection which we nevertheless demonstrated to be present.

TREATMENT. The question of treatment involves numerous considerations. A perinephritic abscess must, of course, be promptly drained, and, if of renal origin, subsequent investigation must determine the fate of the kidney itself. A pyonephrosis commonly requires a nephrectomy. Infected stone kidneys must be dealt with according to circumstances; some have to be excised; in others it is possible, though difficult, to remove the stone, and later on rid the pelvis of its infection by suitable cystoscopic measures. If a stricture of the ureter is associated with a pyelitis it will have to be dilated, and similarly an infection dependent upon prolapsus will necessitate nephropexy.

Cases without these gross complicating lesions present a problem to themselves. As a rule we are reluctant to adopt manipulative procedures in an acutely inflamed urinary tract, but very often we feel that no other recourse is left. The acute coccal infections often, and the acute bacillary infections rarely, reach surgical proportions. The progressive toxemia accompanying the so-called unilateral infarct or the bilateral coccal infection (with preponderance of pathology on one or the other side) may within a few days or hours imperatively demand drainage of cortical abscesses or even nephrectomy. We would, however, advise extreme caution lest we too hastily adopt this irrevocable measure. In many cases such kidneys have an astounding reactive ability, and the patient with almost dramatic suddenness will pass from great danger to comparative safety. Moreover, we will hereafter refuse to recommend or adopt the more radical procedures until a preliminary lavage of the pelvis has been undertaken. We are aware that in this type of infection the inaccessible cortex is chiefly involved and lavage supposed to be of questionable value. However, in several cases (two of them still under treatment) silver nitrate irrigations of the pelvis have aborted attacks which appeared to be imminently demanding nephrectomy. We regret that lack of space prevents detailed reports of these cases. In the last of the series the clinical picture was absolutely classical, including a positive staphylococcus blood culture. Should lavage fail, however, we would then unhesitatingly remove the offending kidney.

When the coccal infection is not of this fulminating type it will generally subside rather promptly, though it will sometimes pass over into a chronic condition. The acute colon bacillus infections will rarely at any time require operative measures; the toxemia here is usually less severe, but there is a much greater tendency of the infection to relapse into the chronic with periodic acute exacerbations. Treatment of the chronic infections and of these latter acute forms may be considered under the same terms. Attention to diet, rest, sleep, fresh air, and general hygiene are important. The most valuable internal medication consists of draughts of pure water. We cannot overestimate the importance of demanding that the

patient systematically flood the urinary tract. Antiseptic drugs have been disappointing. The formaldehyde-carrying formulas (urotropin) have a definite germicidal action in the bladder when properly used, and a similar but vastly less potent action at the level of the pelvis of the kidney. In the substance of the organ where the cocci are lodged they are of no value whatever. The ideal urinary antiseptic has yet to be found; in the meantime we would add methylene blue and quinin to the therapeutic arsenal. Vaccines, autogenous or otherwise, have not proved their case in our hands. Our judgment would instruct us, however, that this is probably less the fault of the vaccine than of our understanding of its proper application. We are rather convinced that vaccines will eventually be of much service in these conditions, and we desire to push our investigations in this direction. The remedy *par excellence* is lavage of the pelvis. We deprecate the discouraging tone of a recent publication.³ Our experience in many cases utterly contradicts the conclusions of this writer. In his opinion kidney infections, curable through pelvic lavage, owe their recovery to catheter dislodgment of material which blocks the lumen of the ureter, and hence he believes that "the less dangerous procedure of simple ureteral catheterization" is equally efficacious. In expert hands a properly conducted lavage is without danger, and in more than 200 pelvic irrigations we have yet to meet a single one of the sequelæ mentioned in this article. Obstructive material has not often been present in the ureter in our cases. Furthermore, in many instances in which we have practised preliminary diagnostic catheterization without lavage, but with theoretical removal of the obstruction, there has been an entire absence of the improvement which has followed later when systematic lavage was undertaken. In brief, our experience, so far as we are concerned, negatives every point advanced by this author.

For lavage we have abandoned all other media in favor of silver nitrate and formaldehyde. Of the two, silver is much the more constantly effective. The precipitate of silver chloride in the urine is disconcerting and has led us from time to time to search for some substitute. Invariably, however, we have been forced by clinical results to return to silver. We have failed to note, however, that the higher percentages (5 per cent.) are of any greater effect than the lower (1 per cent.).

It must be remembered that in spite of all treatment, including lavage, some infections will prove ineradicably rooted in the pelvis. Temporary improvement can often be effected in these cases, and by periodic séances the condition can be held more or less constantly in leash; but a permanent complete cure appears hopeless unless nephrectomy is undertaken.

³ Surg., Gynec. and Obst., January, 1917.