

ASCENDING LYMPHOGENOUS RENAL INFECTION.*

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WE have attempted to study the route of infection of the kidney which takes place in an ascending direction along the interstitial lymphatics of the ureter. A preliminary report of our work was published early in the present year¹ and the complete results of our experiments will be published shortly.²

We have felt for some time that the older view of infections ascending from the bladder to the

kidneys along the lumen of the ureter must be abandoned, except in cases of complete obstruction of the ureters. The work of Sakata, Bauereisen, and Kumita has shown that there is a direct and very intimate connection between the lymphatics of the bladder and those of the ureter and of the latter with those of the renal pelvis and kidney parenchyma. The work of Kumita especially has demonstrated the presence of a network of lymphatics in close relation to the blood vessels within the kidney. This network within the kidney communicates again with the lymphatics of the fatty capsule of the kidney (Fig. 1). In all previous experiments the ureter was either ligated and the organism injected above the point of ligation or the ureter was severed and reimplanted into the intestine. We believe that the ligation method produces a complete obstruction seldom found clinically, while the objection to the reimplantation method

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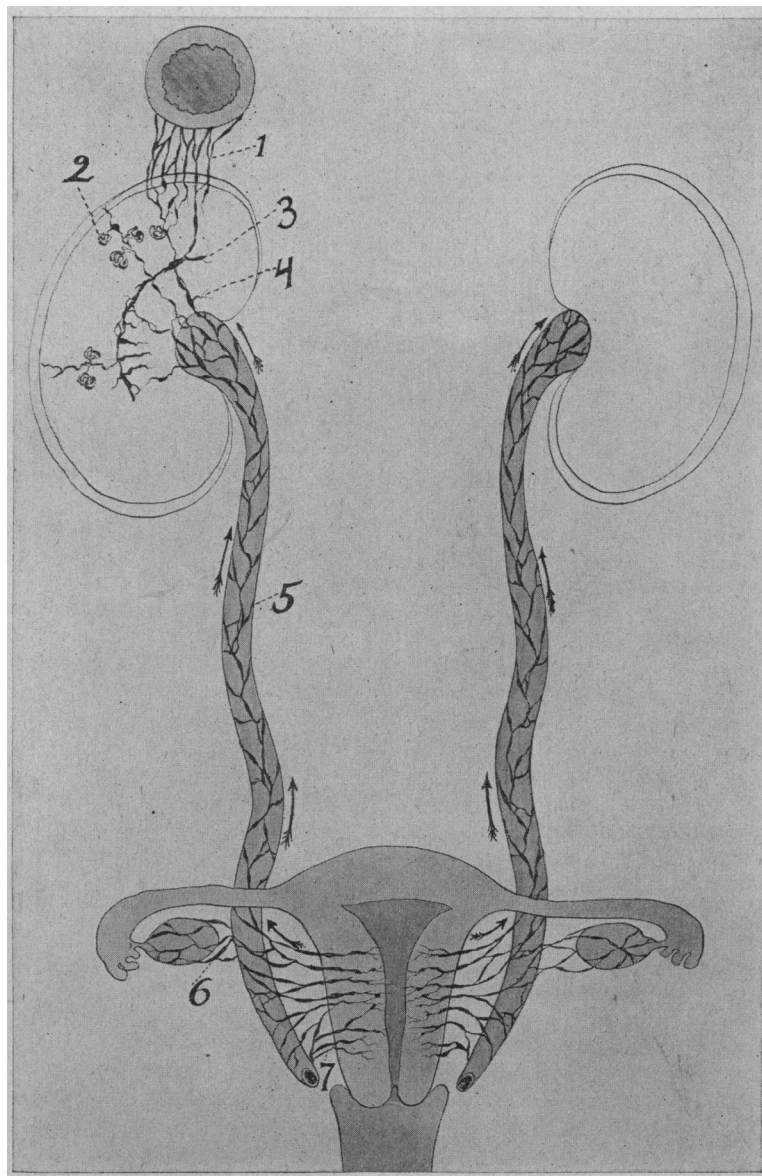


FIG. I.

is that the action of the ureteral sphincter is nullified, and that the opportunity for entrance of organisms into the lymphatics of the cut ends of the ureters allows pathologic changes to occur with such intensity that it is difficult to trace the paths of the infection.

Technic.

The organisms employed were *Bacillus coli*, *Staphylococcus aureus* and *Bacillus proteus*. We attempted to imitate conditions found clinically in cases of ascending renal infection in the human being, by making an emulsion of sterile salt solution and scrapings of four agar slant cultures of the organisms. This emulsion was then injected into the bladders of female animals (dogs and rabbits) through a sterile silver cannula of very narrow caliber. The external genitalia were first thoroughly cleansed and some of the urine obtained for cultures so as to determine whether any infection was present before the emulsion of the bacteria was injected. The animals having been anaesthetized with ether, every precaution was taken to avoid any injury to the mucosa of the bladder and urethra. A minimum degree of force was used in injecting the emulsion.

Our animals were killed at varying intervals with strychnine and cultures were immediately made from the heart's blood, from both kidneys and from the bladder. For microscopic study the urinary tract with the surrounding connective tissue was removed *en masse*. Areas from different portions of the bladder were first taken, then the entire ureter was divided into segments. The lowest segment included the uretero-vesical junction and the highest, the junction of the ureter and renal pelvis. Between these two, the ureter was divided into four segments.

The kidney sections were taken so as to include in one set the areas where the finer divisions of the renal pelvis receive the papillae and in another set as much as possible of the medulla and cortex in a single section. All tissues were imbedded in paraffin, cut serially and stained with hematoxylin and eosin. The various segments of the ureters were cut longitudinally in serial sections, so that one could follow the paths of the infection continuously from the bladder upward into the ureter and along the walls of this structure into the parenchyma of the kidney. We cannot emphasize too strongly the great value of longitudinal serial sections in following the evidences of infection along the lymphatics of the ureter.

In two series of experiments carried out according to this technic, just outlined, a total of thirty-seven animals were used. Of these, eleven were rabbits and twenty-six were dogs. Of the eleven rabbits, six showed involvement of the ureter, five of the pelvis, and six of the kidney. The pathogenic organism injected was recovered from the bladder five times; from the kidney twice.

Of the twenty-six dogs used, twenty-one showed ureteral involvement, sixteen pelvic involvement, and thirteen, lesions of the kidney. The organism injected was recovered from the bladder twelve times and from the kidney five times. Seven dogs were examined by the same method as controls. One of these showed the same type of lesion in the ureter and pelvis.

Microscopic Changes.

Five days after the introduction of the bacteria into the bladder the urinary tract is the seat of a well-marked sub-acute inflammatory reaction, which is chiefly infiltrative in character. The change is most marked in the sub-epithelial tissues of the lower end of the ureter, especially about the mouth of the latter, and in the tissues of the pelvis. At these situations the stroma is decidedly infiltrated with lymphocytes, the endothelium of the lymphatics is swollen and there are numerous foci of perivascular infiltration. The mucosa of the bladder is decidedly infiltrated and in the mucosa and sub-mucosa the lymphocytes are congregated about the vessels. The ureter, between its lower and upper ends, where the reaction is most pronounced, shows moderate paths of lymphoid infiltration of the stroma, epithelium and muscle with some perivascular localization. The same reaction is present in the interstitial stroma of the kidneys leading to the formation of lines or band-like areas of cellular infiltration. The epithelium of the entire tract is intact, except in a few places where it has been invaded by the lymphoid infiltration.

Examination of the serial sections of these areas shows that these foci are largest in the sub-epithelial tissue, indicating that they had their origin here and only secondarily invaded the deeper portion of the epithelial layer. The experiments of longer duration, as compared with the five-day experiments, show those progressive changes in the inflammatory reaction that are to be expected. The sub-epithelial stroma is proliferated throughout the urinary tract from the bladder to the renal pelvis. The older series are more proliferated than in the fifteen-day experiments. New blood vessels are present and the lymphatic endothelium is proliferated. The focal lymphoid infiltration may be present in the bladder mucosa, in the sub-epithelial tissues of the ureter and pelvis. In the pelvis the infiltration may be diffuse as well as focal. The lymphoid infiltration is most marked at the mouth of the ureter and in the pelvis along the middle third of the ureter there may be, scattered, small foci of perivascular infiltration in the tissues of the outer zone of the ureteral wall.

Comparison of the changes due to the three species of the bacterial organisms used shows in the dogs the most marked reaction after *B. coli* and the least marked after *Staphylococcus aureus*, with after *B. proteus* a reaction inter-

mediate between the other two. The findings are at variance with the usual statement that a pyogenic infection produces a most intense localization.

In the rabbits the same virulent reactions were obtained after *B. coli* and *B. proteus* as well as staphylococcus. In the dogs in every case the reaction is characterized by the absence of polymorphonuclear leucocytosis; by diffuse or focal lymphoid infiltration in the early stage, of variable degree, depending upon the organisms; and by moderate proliferation of the sub-epithelial stroma and of the capillaries in the later stages. Always, even when the changes are slight, the endothelium of the lymphatics reacts by swelling and proliferation, which may continue to such a degree that individual lymphatics may become completely filled with large, irregular polyhedral cells. Common to all the experiments is the intact condition of the lining epithelium of the entire tract. In every case the uretero-vesical and the uretero-pelvic junctions show a greater degree of inflammatory reaction than does the rest of the tract.

DISCUSSION OF CLINICAL APPLICATIONS.

Our work shows that both motile and non-motile organisms are easily transported from the bladder to the kidneys by the lymphatic stream in the ureteral wall. This is not dependent upon the presence of any obstruction of the lower urinary tract, and it occurs even with intact uretero-vesical orifices. This would explain many of the cases of pyelitis and pyelonephritis which complicate a cystitis. When fever and chills occur during the course of an infection of the lower urinary tract, it is now generally accepted that this indicates an infection of the upper urinary tract, a pyelonephritis. Our experiments prove conclusively, we believe, that the path along which this infection travels is first in the bladder in the submucous and perivesical lymphatics, then by way of the lymphatics of the ureter (especially the submucous and peri-ureteral) to the submucous lymphatic vessels of the renal pelvis, and from here by continuity of the lymphatics directly into the network of intrarenal lymphatics, and then beyond this, into the perinephritic tissues (through the communication of the lymphatics of the cortex with those of the true and fatty capsule of the kidney).

Although difficult to prove experimentally, we believe that our work shows that the free anastomosis between the lymphatics of the broad ligament and those of the ureter makes it possible for infection to travel directly from the uterus and adnexa to the ureter, and from here to the renal pelvis of the kidney.

The intensity of the pyelitis in some of our dogs was out of all proportion to the ureteral changes. We believe that the same occurs clinically, and is explained by the slowing up of the lymphatic stream just before it communi-

cates with the lymphatic current within the kidney. We have observed the gradual lessening of the intensity of the reaction the longer the animals lived. This is due to the immunization of the animal toward further infection, unless the intra-vesical inoculation is constantly repeated. The same phenomenon is observed clinically. As the infection in the bladder decreases, the pyelitis improves in equal ratio. This explains why bladder irrigations and supra-pubic or perineal drainage cause a rapid improvement in conditions of urinary sepsis, especially in infected kidneys.

CONCLUSIONS.

1. Anatomical studies have demonstrated the presence of an anastomosing network of lymphatics in the wall of the bladder and of the ureter, communicating above with a similar lymphatic network in the renal pelvis and parenchyma. At its lower end this system communicates also with the lymphatics of the pelvic structures, in both the male and female.
2. Infections of the bladder or lower ureter may reach the renal pelvis or the kidney, either by way of the lumen of the urinary tract or by way of the mural lymphatics.
3. Experimental and clinical evidence indicates that almost complete obstruction to the free passage of urine is necessary for ascent of infection by way of the lumen of the urinary tract.
4. Experimentally we have shown that infection, set up by the simple introduction of bacteria into the bladder without injury or without obstruction, may pass upward by means of the interstitial lymphatics of the ureter.
5. The degree of involvement following the introduction of bacteria into the bladder depends upon the virulence of the organism and upon the susceptibility of the animal. The subsequent tissue reaction may remain limited to the bladder and ureter, it may pass upward to the tissues of the renal pelvis, or even the parenchyma of the kidney itself may become involved.
6. When the kidney tissue is involved in ascending infection brought about experimentally, as described, the path of travel is from the sub-epithelial tissues of the pelvis to the kidney by way of the inter-tubular and perivascular lymphatics.
7. From the kidney the perirenal tissues may become involved through the capsular lymphatics, which anastomose with those of the cortex.
8. The experimental evidence indicates that, in cases of pyelitis and pyelonephritis in the human, secondary to infection of the bladder, the lymphatics constitute the most important course of upward travel of the infection, especially in those cases where there is no hindrance to the urinary outflow.
9. Pyelitis and pyelonephritis, not secondary

to cystitis, may also be the result of lymphatic transport of infection from the pelvic organs in the male and female, and from the lower intestinal tract.

REFERENCES.

- ¹ Jour. A. M. A., Vol. lxvi, February, 1916.
² Jour. A. M. A., Vol. lxviii, p. 540, February 17, 1917, and Jour. Med. Research, Vol. xxxv, January, 1917.

DISCUSSION.

DR. HUGH CABOT: This paper raises a very interesting group of questions which are important. I want to thank Dr. Eisendrath for giving us ample opportunity for going over his material in advance. It is certainly in that way that one gets down to the facts, where you can take a man's work and go over it at your leisure. When any one of us puts out work which is at variance with the work of previous observers he will not object to confirmation.

Dr. Eisendrath's method of producing all these infections is by the injection of organisms into the untraumatized bladder. That is a type of experimental work which has been done for years. There is an immense mass of evidence showing that infection of the bladder and the urinary tract cannot be produced by that method, and I submit that there is an inherent possibility of error at this point. There is clinical and an immense mass of experimental evidence tending to show that by the introduction of organisms into the bladder in the absence of obstruction, whether produced experimentally or existing pathologically, no infection has ever been demonstrated to take place, and I think it is certainly necessary that this work be confirmed and that evidence be produced by other experimenters that it is possible to produce inflammatory lesions of the urinary tract without the production either of trauma or obstruction.

In the production of an inflammatory lesion of the urinary tract such that the lesion can be demonstrated and in which the organisms are recovered from the urine at autopsy, it is necessary to show that in the cases where the organisms are recovered there shall be a lesion in that patient. For example, in Case 401, a dog infected with the colon bacillus, there were no lesions and yet the organism was recovered from the bladder. That is a case that requires explanation. Take also Case 429, a dog with the bacillus proteus. There were lesions in the ureter, pelvis and kidney, and no culture. In one case there are lesions and no growth, and in the other, growth and no lesions. Again, the length of time over which these organisms appear to be recoverable seems to me quite extraordinary.

It is acknowledged that the chronic colon bacillus lesion of the kidney is a pyelitis which connects with the urinary tract. That is the lesion typical of pyelitis and has been so recognized for years. The organisms persist because they grow in the urinary tract, either in the mucous membrane or, in the presence of obstruction, in the urine itself. The characteristic thing about Dr. Eisendrath's lesions is that they are not in contact with the urinary stream and we should not expect to find organisms in culture in the urine.

It is interesting, I think, to trace the cause, the natural history, as one might say, of a case of pyelitis. The early cases have been difficult to find. There is very little pathological material other than experimental material showing the exact nature of the colon bacillus infection, which later may termin-

ate fatally. Now those specimens, as far as I have known of them, have universally shown a pyelitis demonstrated by the organism in the mucous membrane and in infiltration of the mucous membrane, the process having settled there because that is a satisfactory medium for it, whereas the kidney itself is not a satisfactory medium. The organisms enter the kidney from above and infect it. They do not find a location favorable for growth and ultimately arrive at the mucous membrane and do find there a congenial condition, so there they remain. That is, as I believe, the typical cause of colon bacillus pyelitis.

Dr. Eisendrath says that this work shows the transference of organisms from the bladder up along the ureter to the kidney. I submit that no transference is shown. Perhaps he has slides which show organisms, but if so we have not seen them. It seems to me absolutely essential that if it is to be claimed, as he claims, that he has demonstrated the transference through the bladder to the kidney, the organism would be somewhere along the road. Organisms in these lesions must be shown if we are to believe that the organism and the lesion are fastened together.

I understood him to correlate the occurrence of fever and chills in a case of acute pyelitis subsequent to a cystitis with the passage of the organism along the lymphatics. One might suggest that fever and chills are commonly produced by the entrance of organisms into the blood stream, and the colon bacillus has been found in the circulation with great regularity. It is not safe to assume that fever and chills occurring in pyelitis are due to lymphatic infection. They certainly may reach the kidney through the blood stream.

Again, I think one does well to remember that the lymphatic systems of the ureter are exceedingly segmented. There is nothing, as far as I know, approaching a continuous chain of lymphatics for any considerable distance. They leave the region of the ureter and go to the lymph nodes. They must return back along the lymphatics from the nodes to the ureter. It is not a continuous performance, by any means. We must be prepared to assume that they leave the ureter and then see fit to return to the ureter in preference to staying where they are.

Again, we should do well to remember that where, as is shown here, there are areas of definite infiltration about the blood vessels, it does not follow that those are lesions of the lymphatics. We know, in fact, that lesions of the vein will produce that appearance about the vein involved, and that a perivascular infiltration does not by any means show it to be lymphatic and in some cases clearly does show it to be vascular in origin. Undoubtedly organisms leave the vein and reach the lymphatic, and *vice versa*, once having been in a lymphatic, very readily enter blood vessels. It may be readily interrupted at any point in its progress by direct entrance into the vein.

Then finally (and I trespass here slightly on the ground which Dr. Crabtree will cover), lymphatic infiltration is not characteristic of any inflammation known to be produced by the *Staphylococcus aureus*. It is quite at variance with human microscopic pathology, and is evidence of a chronic and not of an acute lesion.

We must hold that this is an interesting piece of work, that though it shows lesions in the peri-ureteral, peri-vesical and peri-pelvic structures,