ON ARTIFICIAL BLADDER WITH SPECIAL REFERENCE TO HISTOLOGICAL STUDY

by

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INTRODUCTION

Recently chances of pelvic surgery have gradually increased, especially those of total cystectomy and pelvic evisceration, supported by advances in pre- and post-operative treatment and development of anesthesia. However, surgeons inevitably encounter an unsolved problem of urinary diversion in this area of pelvic surgery—it is a main part in the operation, and in addition, it has a severe influence upon the prognosis of the patient. This urinary diversion has been studied ever since about the middle of the last century in Europe and America; and various methods have been devised and tried both experimentally and clinically. However, HINMAN and SMITH (1939) reported that the number of cases in which total cystectomy was performed, was only 254 during 52 years, from 1887, when Bardenheuer reported the first case, to 1939. Orr, CARSON and NOVAK (1939) reported also that total cystectomy and ureterointestinal anastomosis were performed in only 1.35% cases of cancer of the bladder. Even though cases of total cystectomy are developing a tendency to increase at present, it is not performed so frequently. Why is it that cases of cystectomy are few, notwithstanding a strong social demand for it? HIGGINS (1938) answered the question as follows: "it is not because of the difficulty of operative technique, but because of the diversity of opinions of the surgeons as to the definite method of urinary diversion after cystectomy." That is, the ideal method of urinary diversion has not been discovered yet.

Therefore, I feel it is necessary to review historically reports on the problem that have been published till present. They can be classified largely into 4 categories.

1. *Ureterocolostomy into the Intact Colon*

JOHN SIMON (1851) tried to make fistulous communication between the ureters and the rectum in a case of exstrophy of the bladder. But the patient died of ureterorenal and peritoneal inflammation after 1 year. LLOID (1851) also tried the same operation for exstrophy of the bladder and lost the patient on account of panperitonitis on 8th postoperative day. KÜSTER (1891) reported the first clinical case in which ureterorectal transplantation had been carried out after cystectomy. Following these pioneers, especially after COFFEY's submucosal tunneling method appeared, ureterocolostomy has been frequently applied clinically. But the procedure

is inevitably accompanied by such fatal complications as hyperchloremic acidosis, obstruction of ureteral stoma, ascending infection and others.

2. *External Ureterostomy*

Ureterocutaneostomy, pyelostomy and wet colostomy are included in this group. WASSELJEW (1893) performed for the first time ureterocutaneostomy after cystectomy. As a variation of this method, PAWLICK (1889) performed the first successful cystectomy on a woman, transplanting ureters into the vagina on 24th day after cystectomy, and enabled the patient to be alive for 16 years.

Though ureterocutaneostomy is not only palliative but liable to be accompanied by such complications as ureteral obstruction and ascending renal infection, surgeons like to adopt this procedure because it is simplest. Wet colostomy consists of implantation of the ureters into the descending colon just proximal to the colostomy. BRUNSCHWIG (1948) performed this procedure on 22 cases of advanced carcinoma of various pelvic organs, combined with pelvic evisceration, recording 2 years as the longest survival period. This procedure, however, is seldom performed because of its difficulty in management and the hazards of causing obstruction or ascending infection, of the urinary tract.

3. *A Segment of the Digestive Tract used as a Urinary Way*

In this method, an isolated intestinal segment with implanted ureters is used as a substitute bladder or a urinary reservoir and the one end of the segment is brought either out of the abdominal wall or through anus, without utilizing the urethra. MAUCLAIRE (1895), using dogs, transplanted the ureters into the isolated rectum and brought the distal end of the sigmoid out of the skin in the ilac region. Also he advised clinically a perineal anus. This was performed by REMEDI (1905), but the patient died of urinary obstruction and infection on 4th postoperative day. KRONIG (1907) performed the same operation in 3 stages and the patient could live for more than 5 years. PAYR (1914) performed this procedure in one stage upon 2 patients with bladder or uterus cancer, both surviving for several months. GERSUNY (1898) and HEITZ-BOYER (1910), trying to establish fecal as well as urinary continence, brought down the sigmoidal stump anterior or posterior to the rectal bladder and anchored it within the anal sphincter.

Thereafter many surgeons published clinical reports following this procedure. VERHOOGEN (1908) used the ileocecal section as a urinary reservoir and utilized the appendix as urethra, bringing the latter out of right inguinal region. MUKKAS (1910) applied first this method clinically, and since then many surgeons followed him successfully. Recently, BRICKER, EISMAN (1950) and MERRICKS (1951) were successful in utilizing a similar technique clinically, excepting that the terminal ileum was used as a urethra. BACKER (1956) also reported 20 cases in which the terminal ileum was used as a urinary reservoir. In cases these operative procedures are performed, ascending infection and absorption of urinary elements will be much reduced, but urinary incontinence can never be avoided.

4. *Ureteroenterourethrostomy using an Isolated Intestinal Segment*

Tizzoni and Foggi (1888) first performed experimentally ureteroileourethrostomy following total cystectomy, reporting that experimental animals had been continent in urination and well even after 2 months. Lemoine (1912) performed a simiar procedure clinically. He used, as a urinary reservoir, the excluded rectum which was anastomosed to the urethra, and the distal end of the sigmoid was anastomosed to the anus. Thus he established urinary and fecal continence, respectively, with the urethral and rectal sphincter for control, losing the patient on account of septicemia on 18th postoperative day. In 1943, Bisgard performed ureterosigmoidourethrostomy experimentally in 2 stages procedure using an isolated sigmoidal segment. Rubin (1948) and Thompson (1950) also performed the same experiment. They obtained a continent substitute bladder using the urethral sphincter, and could prevent ascending infection by combined use of antibiotics. However, a moderate amount of mucus was secreted out from the mucosal surface of the segment which was used as a substitute bladder, and this fact involved always danger of both obstruction and infection. Therefore, Shoemaker and his co-workers (1955) performed substotal cystectomy on dogs, and repaired the bladder defect with inverted seromuscular graft of ileal loop. They reported that the vesical function was satisfactory 4 months postoperatively, but in cases in which total cystectomy had been performed, the results were not completely satisfactory. Bohne (1955) tried to regenerate the bladder following total cystectomy by using an acrylic mold with ureterourethral splint, enabling the dog to survive for 9 months.

Those which are included in the above mentioned 1, 2 and 3 categories have some intractable complications, such as serious ascending renal infection, reabsorption of urinary elements or urinary incontinence. Therefore, application of these procedures is so much limited that surgeons hesitate to perform cystectomy, and even nowadays palliative treatments are often seen to be performed, which can be called a hopeless operation upon a hopeless patient. We surgeons, however, are never satisfied with the present status, but always have to exert ourselves, taking aim at an ideal method.

Now, I have tried 2 kinds of experiment to make an artificial bladder which will satisfy the following items;

1) maintaining natural continuity of the urinary tract,
2) decreasing ascending infection as much as possible,
3) maintaining urinary continence without hyperchloremic acidosis, and
4) making postoperative instrumentation easy.

My experiments consisted of (i) ureteroileourethrostomy, using an isolated ileal segment as a substitute bladder, and (ii) regeneration of the bladder using a resin mold or a polyvinyl formal mold, following total cystectomy.

MATERIAL AND OPERATIVE PROCEDURE

I. Ileum Bladder (Ureteroileourethrostomy) (Fig. 1).

Fifteen female adult dogs were used, which weighed from 8 to 15kg. It is simply because female dogs are easier to operate, and also to manage postoperatively

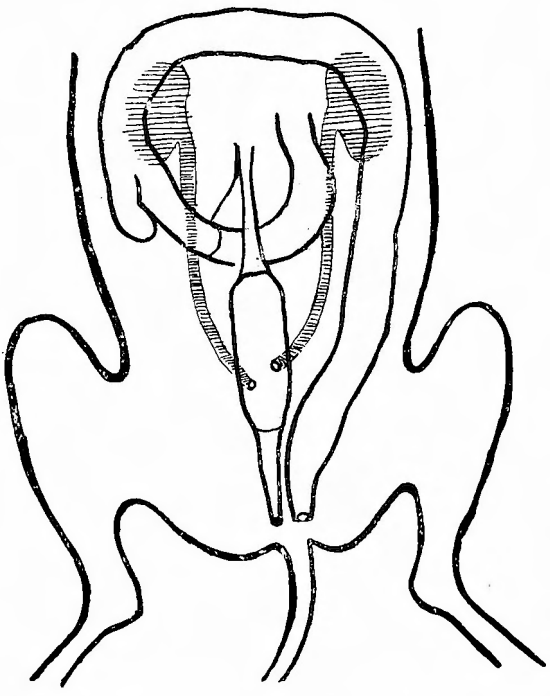


Fig. 1. Ureteroileourethrostomy, performed on group-A and-B.

that female dogs alone were used. Intestinal antiseptics were not administered at all preoperatively. The dogs were fed with ordinary diet till the day before the operation and only on the very day of the operation, they were put to fasting from the morning.

The dog was anesthetized intravenously with 2.5% solution of sodium pentothal and was fixed on the operating table. The abdomen was prepared and draped.

A suprapubic midline incision was employed under sterile technique. After opening the abdominal cavity, a suitable segment of terminal ileum was isolated together with its intact mesentery. A segment of about 10 cm was used because of the fact that the shorter it is, the less electrolytes in urine it absorbs The continuity of the terminal ileum was re-established. The isolated ileal segment was washed several times with sterile saline solution to remove the mucus on its surface. After washing, the distal end of the isolated ileal segment was closed.

Next, the bladder was drawn out of abdominal cavity with bladder forceps. The ureters were identified and cut free just before they entered the bladder. Then terminal portions of bilateral ureters were mobilized for a distance of 5 to 10 cm respectively by means of blunt dissection from the surrounding retroperitoneum. Through out these procedures, cares were taken to avoid any injury to supplying blood vessels. Then the bladder was extirpated at the posterior urethra or at the vesicourethral juncture, after complete ligation and dissection of its supplying blood vessels. A small incision was made on both sides of the ileal segment in order to transplant the ureters into it. The open end of the ileal segment was then anastomosed to the urethral stump. After completing the posterior half of the ileourethrostomy, a ureterourethral catheter was inserted and the distal end of the urethral catheter was brought out from the external urethral orifice and proximal portions of the ureteral catheters were drawn out of the lumen of the ileal segment respectively through small incisions. Bilateral ureteral catheters were inserted into bilateral ureters respectively and the ureters were transplanted into the segment. At last, the ileourethrostomy was completed anteriorly. Two hundred thousand units of penicillin and 1 gm of streptomycin were instilled into the abdominal cavity. The abdominal wall was closed and the distal end of the

urethral catheter which had been brought out the external urethral orifice, was fixed to the vaginal wall. In this experiment, Coffey's submucosal tunneling method was performed on 2 ureters of one dog, Kerr and Colby's method on 8 ureters of 4 dogs, and full-thickness end-to-side anastomosis on 22 ureters of 11 dogs.

II. Regeneration of the Bladder.

In this experiment, 14 female adult dogs 7 to 14 kg were used. The bladder was regenerated from the perivesical fatty tissue, by support of a hollow resin solid mold of 20 to 30 cc in volume or polyvinyl formal mold of 15 to 25 cc in volume.

The dog was prepared and anesthetized as mentioned above. The operative procedures consisted of 2 stages, that is, insertion of a mold and removal of it. In the first stage, the abdominal cavity was opened by means of a suprapubic midline incision. Total cystectomy was performed, taking care to leave the perivesical fatty tissue as much as possible. Then ureteral and urethral catheters which were attached to the mold were inserted into the ureters and the urethra respectively, to be fixed to them; and the mold was wrapped up so closely with the perivesical fatty tissue that it might be perfectly shut out of the free peritoneal cavity (Fig. 2). When the perivesical fatty tissue was not enough, the uterine late ligament was used for wrapping. The abdominal wall was then closed after some antibiotics were administered intraperitoneally.

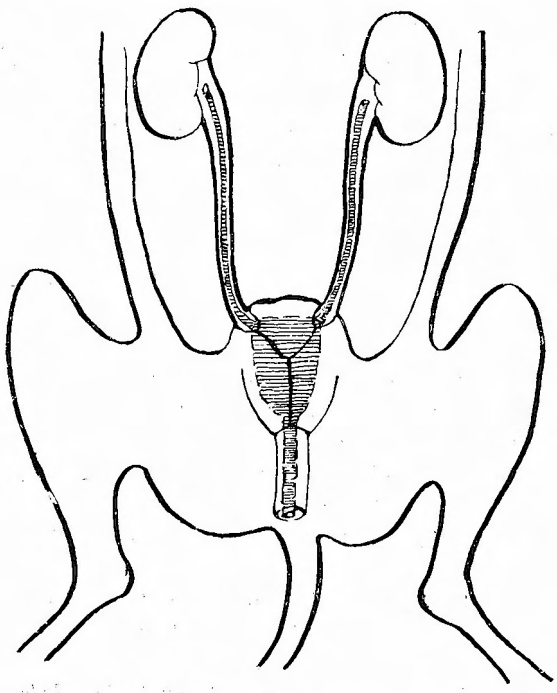


Fig. 2. The first stage produre in regeneration of the bladder.

The second stage procedure was performed about 7 to 8 weeks after the first operation. In this stage, the peritoneal cavity was opened through the former operation scar and the anterior wall of the regenerated bladder was opened carefully, to remove the mold and to insert a ureterourethral catheter in its place, which was fixed to the external urethral orifice. Some antibiotics were also instilled both into the lumen of the regenerated bladder and the abdominal cavity, to be closed thereafter.

METHODS OF LABORATORY WORKS

Thes experimental animals were observed periodically in the laboratory by means of various tests, that is, phenolsulphophthalein excretory examination, estimation of blood electrolytes, excretory urography, retrograde cystography and

cystometry. These methods and their results are described in details in the papers of my co-workers, N. SANO, T. TSUDA and Ch. IWADE.

The histological study was the main subject in this article. Autopsy of experimental animals was necessarily performed when they died or sacrificed, to make a histopathological survey of the materials, such as the junction of ureteroileostomy, ileourethrostomy, the substitute bladder wall, the regenerated bladder wall and the kidneys. Various stains of the microscopic sections were used as follows; i) Hematoxylin-eosin stain, and ii) Van GIESON's stain were performed on all sections, and iii), in addition, on sections of ileum bladder alone, mucicarmin stain was applied. On some long term survival cases, adaptation or alternation of smooth muscle fibers of the substitute bladder wall was observed with micrometric examination as follows, being controlled with the normal ileum. The dog being sacrificed, a small piece of specimen was taken both from the substitute ileum bladder and from the terminal ileum, of which mucosa and serosa were completely stripped away, only the muscle layer being left. The muscle layers were seperated with forceps into several pieces, which were put into a test tube with 5 cc of 20% HCl solution to be incubated at 37°C for 5 to 6 hours. Thereafter the supernatant HCl solution was washed away, leaving the muscle pieces to be washed again several times with distilled water and to be left for 5 to 10 minutes in 2 to 3 cc of distilled water. Then the test tube was slightly shaken for 5 to 10 minutes continuously till the water in it appeared turbid. A few drops of this turbid content were placed as a smear on each object glass, to be exsicated spontaneously in room air, then fixed and stained with Hematoxylin-eosin.

Under high magnification with a micrometer, straight and long spindle-shaped muscle fibers were selected, of which length and width in 50 were measured and the mean value of each group was culculated respectively, the data of the substitute bladder being compared with those of the normal ileum.

RESULTS

I. *Lleum Bladder.*

Among all the 15 cases, one dog died of anesthesia (C_1), 2 dogs of postoperative management failure (A_3 and B_1), 3 dogs of ascending renal infection (A_1, A_2 and A_3), one dog of intestinal obstruction (A_4), 2 dogs of infectious diseases (C_2 and C_3). One dog escaped on 165-th postoperative day (B_5). As for the remaining 5 dogs, they were sacrificed on 16th, 30th, 82nd, 98th and 311th postoperative day (A_5, B_2, B_3, B_6 and C_4) respectively.

These 15 dogs were divided into 3 groups, that is, A, B and C, according to the operative procedure.

Group-A: In this group, an isolated ileal segment into which both ureters had been transplanted was antiperistaltically anastomosed to the urethra following total cystectomy including the urethral sphincter.

On all cases of this group, partial urinary incontinence was recognzied through the whole postoperative course.

1. Dog A_1, female, 14.5 kg of body weight. The operation was performed on December 10, 1955, according to the procedure mentioned above. In this case, an isolated ileal segment of 20 cm in length and 42 cc in capacity was used, and ureteroileostomy was performed by

COFFEY's method. The dog could not sufficiently recover from the surgery, and died on 13th postoperative day. At autopsy, the site of ileourethrostomy was smooth. The bilateral ureteral stumps formed nodules and the ureteral orifices showed marked stenosis. Consequently a moderate pyohydronephrosis was noticed on both sides. Microscopically, the site of ileourethrostomy showed primary healing and was lined with urcepithelium. The ureteral stumps became edematous and was covered with inflammatory membrane (Fig. 3). There was no change on the wall of the isolated ileal segment. Both kidneys had severe inflammatory changes.

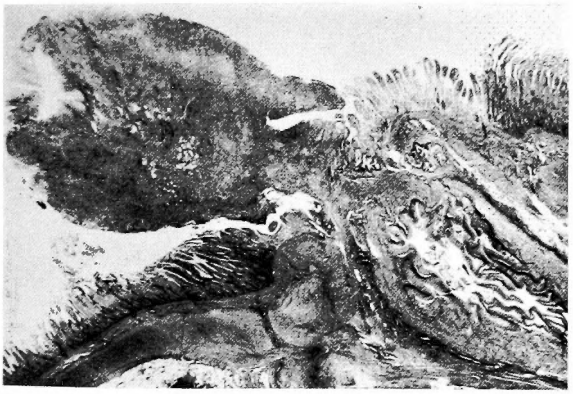


Fig. 3. Ureteral stump forms edematous nodule, covered with inflammatory membrane. The ureteral orifiice shows marked stenosis (Hematoxylin-eosin stain, ×10.)

2. Dog A_2, female, 12 kg of body weight. The operation was performed on December 15, 1955. An isolated ileal segment of 10cm in length and 20 cc in capacity being used, ureteroileostomy was performed by means of KERR and COLBY's method. Postoperative course was good and the ureterourethral catheter was removed on 11th postoperative day. But from about 4th week the dog began to suffer from anorexia and was emaciated gradually and died on 29th postoperative day. Autopsy revealed panperitonitis due to insufficiency of the left ureteroileostomy. The ileum bladder dilated slightly and contained a great deal of mucus. The ureteral orifices showed stenosis, causing pyohydronephrosis on both sides.

Microscopically, the site of ileourethrostomy healed primarily and its surface was lined with uroepithelium. A rosette formed at the left ureteral orifice consisted chiefly of proliferation of connective tissue from ureteral adventitia, and its surface was lined with transitional epithelium. There was a great many goblet cells in the mucosa of the ileum bladder. Sections of the kidneys revealed wide belt-shaped and advanced inflammatory lesions including both cortex and medulla, where some of tubules contained mass of granulocytes.

3. Dog A_3, female, 13.5 kg of body weight. The operation was performed on December 22, 1955. An isolated ileal segment of 8 cm in length and 18 cc in capacity was used, and ureteroileostomy was performed also by means of KERR and COLBY's method, removing the ureterourethral catheter on 5th postoperative day. General condition of the dog was satisfactory early after the operation. But at the end of 4th postoperative week, the perineum was ulcerated owing to continuous partial incontinence, and unfortunately, the dog died of peritonitis due to accidental intestinal perforation on 34th postoperative day. At autopsy, there was a small perforation wound in the intestinal wall about 10 cm proximally from ileal end, and a bamboo skewer was found in the abdominal cavity. The lumen of the ileum bladder contained moderate amount of mucus. A rosette had been formed also around the orifices of both ureters without any stenosis or hydronephrosis (Fig. 4). Microscopically, the site of ileourethrostomy underwent primary healing, and its surface was lined with uroepithelium. The rosette at the ureteral stoma consisted of proliferation of the connective tissue (Fig 5). The mucosa of the ileum bladder and kidneys showed no remarkable change.

4. Dog A_4, female, 12 kg of body weight. The usual operative procedure was performed on January 31, 1956. An isolated ileal segment of 9 cm in length and 14 cc in capacity being used, ureteroileostomy was performed also by means of KERR and COLBY's method. The

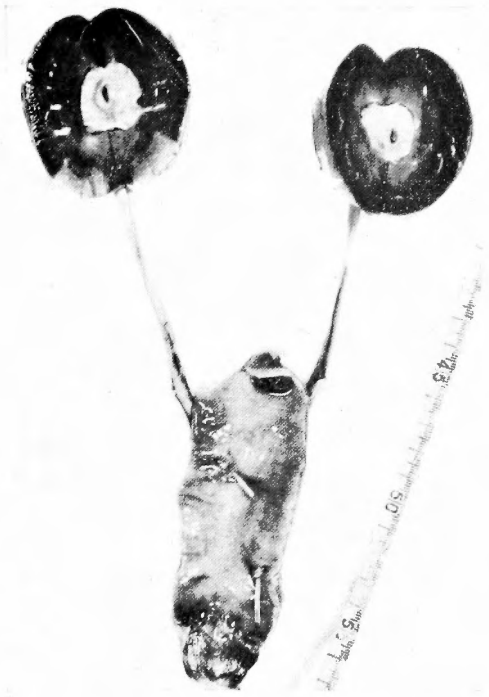


Fig. 4. Dog A_3. Autopsy specimen. A rosette is formed around the orifices of both ureters, but there is no sign of hydor nephrosis.

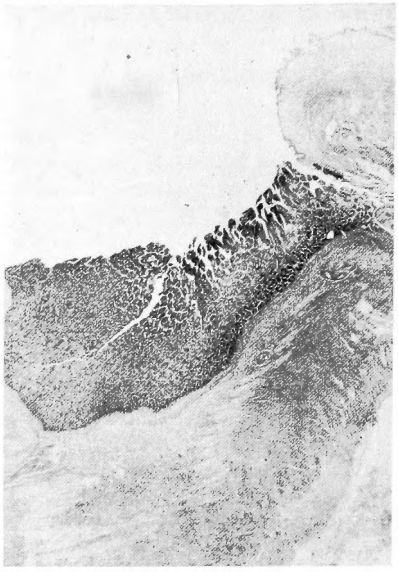


Fig. 5. Longitudinal section through ureteral orifice. The rosette of ureteral orfice consists of proliferated fibrous connective tissue out of ureteral adventitia and of ileal submucosa. The surface of the rosette of is lined with transitional epithelium (Hematoxylin-eosin stain, ×10.)

ureterourethral catheter fell off on 2nd postoperative day. But in 4th postoperative week, there was frequent voluntary urination of about 30 cc even with incontinence, and in 5th week, an ulcer began to develop in the perineal region owing to contamination. Since 5th postoperative week, the dog lost appetite, began to vomit, and died of general prostration on 41st postoperative day.

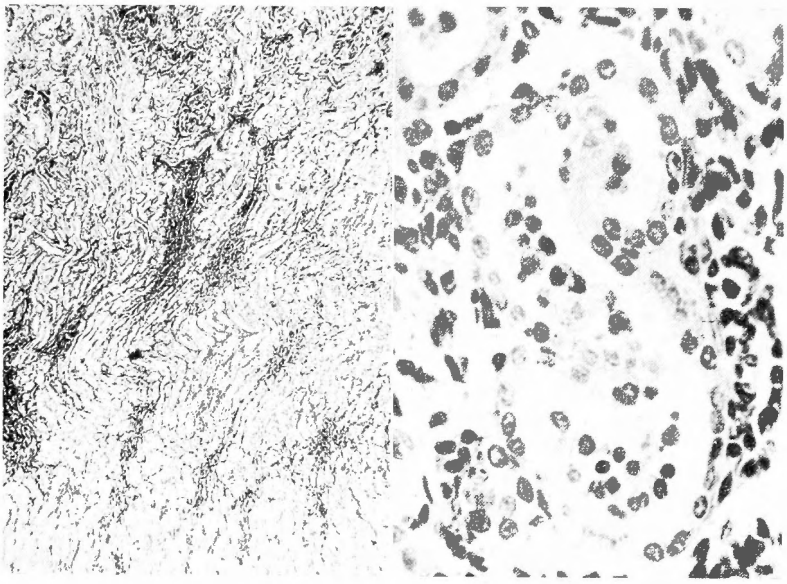
At autopsy, the terminal ileum was strangulated by mesentery of the isolated ileal segment. Both of the ureters were so near implanted to each other that the ileum bladder was strictured at that site. A rosette was formed at both ureteral orifices, which were slightly strictured without any sign of hydronephrosis. The results of histological examination were similar to those of the previous cases.

5. Dog A_5, female, 8.5 kg of body weight. The usual operative procedure was performed on August 11, 1956. An isolated ileal segment of 10 cm in length and 20 cc in capacity was used, and ureteroileostomy was peformed by full-thickness end-to-side anatomosis. Preoperative blood chloride and nonprotein nitrogen were 400 mg/dl and 32 mg/dl respectively, increasing to 420 mg/dl and 82 mg/dl on 4th day. They decreased gradually thereafter and at the end of 3rd week showed 400 mg/dl and 37 mg/dl respectively, and body weight of the dog recovered almost up to the preoperative level. In 7th postoperative week, even though incontinent, the dog voided voluntarily about 30 cc of urine mixed with mucus at intervals of 30 to 60 minutes, and cystometry examination revealed the capacity of the reconstructed bladder to be 50 cc. But in 10th postoperative week, the dog lost appetite slightly, evacuated loose stool, and seemed to be thirsty; it was sacrificed on 85th postoperative day.

Autopsy findings: there was no evidence of peritonitis and intestinal adhesion. The ileum

bladder slightly enlarged and its lumen contained a moderate amount of mucus. Both the ureteral orifices were patent, had no rosette, and were flush with mucosa of the ileum bladder. There were hydronephrosis and hydroureter only on the right side. But both renal pelves contained retrograded mucus.

Microscopic findings: Ileourethrostomy was completed sufficiently and its luminal surface was already lined with transitional epithelium. The urethra revealed a sign of chronic inflammation. The site of ureteroileostomy showed no fibrosis and muscle layers of the ureter and the ileum established complete continuity. Muscle layers of the ileum bladder wall were 1.5 times as thick as normal and villi of its mucosa showed slight proliferation of interstitial cells and infiltration of round cells, but mucosal epithelium showed no change. Sections of both kidneys showed evidence of mild infection (Fig. 6).



A B

Fig. 6. Section of the kidney shows evidence of mild infection. Inflammatory lesions are comparatively localized. A: there is remarkable interstitial cell infiltration, chiefly in the medulla (Hematoxylin-eosin stain, ×50). B: lumen of some tubules containsmass of leucocytes (Hematoxylin-eosin stain, ×400).

Group-B: In this group, the same operative procedure as group-A was also performed, the urethral sphincter being preserved in the total cystectomy.

6. Dog B_1, female, 13kg of body weight. The usual operative procedure was performed on February 8, 1956. An isolated ileal segment of 10 cm in length and 16 cc in capacity was used, and ureteroileostomy was performed by full-thickness end-to-side anastomosis. For several postoperative days, the dog was incontinent in urination, recovering its continence gradually. It went on well subsequently, but on 13th postopetative day, died of an accidental strangulation of the chain around its own neck.

7. Dog B_2, female, 13 kg of body weight. The dog was operated upon March 31, 1956. An isolated ileal segment of 9 cm in length and 14 cc in capacity was used, and full-thickness end-to-side ureteroileostomy was performed. The dog showed slight urinary incontinence postoperatively, but since 5th postoperative day, the urination of the animal became continent and she went on well, being sacrificed on 13th postoperative day. At autopsy, the ileum

bladder enlarged slightly, containing a moderate amount of mucus, with patent ureteral orifices. Neither of the kidneys showed any change.

Microscopically, the uretero-and urethro-ileostomies were completed primarily and were lined with uroepithelium. There was no remarkable change in sections of the ileal segment and the kidneys.

8. Dog B_3, female, 9 kg of body weight. The usual operative procedure was performed on March 27, 1956. An isolated ileal segment of 10 cm in length and 16 cc in capacity was used, and ureteroileostomy was performed by full-thickness end-to-side anastomosis, removing the ureterourethral catheter on 5th postoperative day. At the end of lst week the urination of the dog became continent, and at the end of 3rd week, it voided about 25 cc of urine voluntarily at intervals of 20 to 30 minutes, but its expelling power was weak and it took a pretty long time to void urine. On 28th postoperative day, an excretory urography was performed, which showed no change in the upper urinary tract. Blood chloride and nonprotein nitrogen were slightly higher than the preoperative value through the whole postoperative course. On 30th day, the dog was sacrificed, though it was in good health.

At autopsy, the capacity of the ileum bladder was about 30 cc and its wall was slightly thickened. The junctions of uretero-and urethro-ileostomies were smooth. Both kidneys appeared normal (Fig. 7).

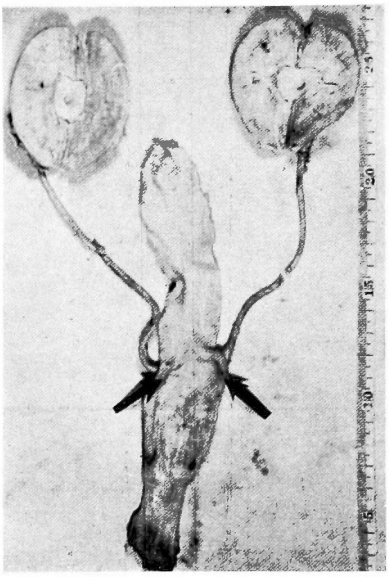


Fig. 7. Dog B_3. Autopsy specimen. Junctions of uretero- and urethro-ileostomies are smooth. Arrows demonstrate the ureteral orifices, which are quite patent and flush with mucosa of the ileum bladder, and both kidneys appear normal.

Microscopically, the sites of uretero-and urethro-ileostomies showed primary healing and were covered with transitional epithelium. There was no remarkable change in the ileum bladder mucosa and the kidneys.

In this case, micrometry of smooth muscle fibers of the ileum bladder wall was performed. The longest of them was 536μ and the shortest 245μ; the widest was 12μ and the narrowest 5μ. The mean values were 398.5μ in length, 8.7μ in width, respectively. The longest muscle fiber of terminal ileum, used as a control, of the same dog was 110μ the shortest 205μ, the widest 9μ and the narrowest 4μ; the mean values were 312.4μ in length, 7.1μ in width, respectively. Accordingly, muscle fibers of ileum-bladder hypertrophied 1.27 times as long, and 1.22 times as wide, as the control.

9. Dog B_4, female, 13 kg of body weight. The usual operation was performed on February 7, 1956. An isolated ileal segment of 12 cm in length and 24 cc in capacity was used, and ureters were transplanted into the ileum segment by means of KERR and COLBY'S method. At the end of lst postoperative week, the catheter was removed. In 2nd week, urination of the dog became continent. On 14th postoperative day, an excretory urography was performed, demonstrating slight hydronephrosis on both sides. Since then the dog seemed to be in good condition, but in 4th week, began to lose appetite gradually and to evacuate loose stool. Ultimately on 35th postoperative day, the dog became extremely emaciated and died. Blood chloride and nonprotein nitrogen showed

moderate elevation through the whole postoperative course.

Autopsy revealed that the right ureter widely adhered to the anterior wall of the ileum bladder and the oral part of the bladder dilated extremely. The capacity of the newly reconstructed bladder was 50 cc. Intraluminal portions of the ureters formed nodule and ureteral stomata showed marked stenosis. Consequently both kidneys showed pyohydronephrosis.

Microscopically, the nodule of intraluminal portions of the ureters consisted of proliferation of fibrous connective tissue originated from the ureteral adventitia. Both mucosa and muscle layer of the segment decreased their thickness, without any change of the mucosal epithelium. Both kidneys showed also the same changes as those of Dog A_2, with advanced inflammatory lesions.

10. Dog B_5, female, 10.5 kg of body weight. The usual operative procedure was performed on March 30, 1956. An isolated ileal segment of 12 cm in length and 18 cc in capacity was used, and ureteroileostomy was performed by full-thickness end-to-side anastomosis, removing the ureterourethral catheter on 3rd postoperative day. At the end of lst postoperative week the dog's urination became continent and it voided freqnently about 20 cc of urine mixed with mucus. At the end of lst postoperative month, the capacity of the ileum bladder was examined under general anesthesia and was found to be 50 cc. In 7th postoperative week, an excretory urogram showed no change of the upper urinary tract. At the end of 5th month, the capacity of the ileum bladder increased to 86 cc leaving several cc residual urine; the dog voided 40 to 60 cc urine at intervals of an hour. But the dog escaped on 165th postoperative day.

11. Dog B_6, female, 12 kg of body weight. The usual operative procedure was performed following cystectomy in which a small area of the bladder neck was preserved, on February 11, 1956. An isolated ileal segment of 10 cm in length and 18 cc in capacity was used, and a ureteroileostomy was performed by fullthickness end-to-side anastomosis, without any use of ureterourethral catheter. Postoperative urination of the dog was slightly incontinent, to be recovered to continence on 5th postoperative day with improved general condititon. Blood chloride and nonprotein nitrogen which had temporarily risen after operation, lowered gradually and at the end of lst postoperative month, they had been reduced to almost the normal level. The animal voided about 30 cc urine voluntarily at intervals of about 30 minutes, which was gradually prolonged, with increased quantity of urine. The capacity of the ileum bladder increased to 100 cc at the end of 2nd month, 140 cc at the end of 3rd month, 280 cc at the end of 6th month, and at the end of 8th month showed 270 cc with 30 cc residual urine and relatively prolonged urination time. Cystography performed at the beginning of 9th month showed not only normal peristaltic movement of the ileum bladder, but also dilatation and reflux of the ureters and the renal pelves. Since 2nd postoperative month blood chloride and nonprotein nitrogen, even with occasional slight rise, kept their normal level all through the course. The dog was in very good health till she was sacrificed on 311th postoperative day.

Autopsy Findings: the ileal segment dilated and thickened remarkably; its diameter was 3 times as wide and the wall twice as thick as the normal ileum. The lumimal surface of ileum bladder was covered with mucus. The sites of uretero-and urethro-ileostomies were smooth and almost indistinguishable.

The ureteral orifices were patent, without any rosette or stricture. The lumens of both ureters were dilated, of which wall showed a remarkable thickening with moderate hydronephrosis on the left side, and marked one on the right side. Renal pelves contained retrograded mucus (Fig. 8).

Microscopic findings: the anastomosis between the bladder neck and the ileal segment was sufficiently completed and indistinguishable, with muscle layers united closely (Fig. 9A). The portion which was suggested to be the site of anastomosis, was lined with ileal mucosa (Fig.

9B). The remaining bladder neck and the urethra showed appearance of chronic inflammation (Fig. 9C). The site of ureteroileostomy was smoothly connected with slight fibrosis, and both muscle layers were also united completely, and the luminal surface was covered closely with ileal mucosa. The ureteral wall was thickened markedly (Fig. 10). The mucosa of ileum bladder showed no change at all, and contained numerous goblet cells suggesting active secretion (Fig. 11). Sections of the kidneys revealed chronic inflammatory lesions of belt-shape including medulla and cortex, accompanied by round cell infiltration, proliferation of interstitial cells and diversity of the size of glomeruli. These changes were more remarkable on the right side than on the left.

The micrometry of muscle fibers of ileum bladder wall was performed, resulting in the longest 735μ (control: 406μ), the shortest 336μ (control: 210μ); the widest 15μ(control: 10.5μ), and the narrowest 7μ (control: 3.5μ) the mean value 552.1μ (control: 305.8μ) in length and 10.8μ (control: 6.4μ) in width. These findings show that muscle fibers of ileum bladder have hypertrophied 1.80 times as long, and 1.69 times as wide, as the control.

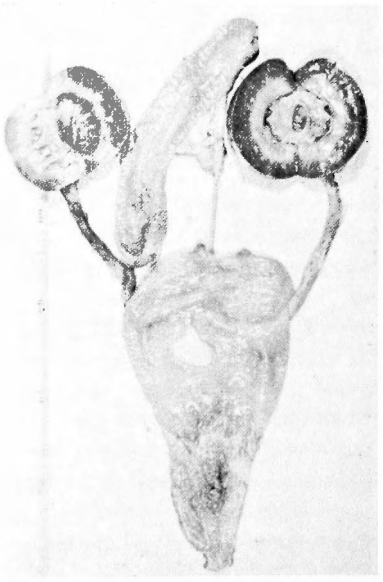


Fig. 8. Dog B_6. Autopsy specimen. The ileum bladder dilates markedly, its diameter is 3 times as long as the normal ileum. Ureteral orifices are patent, but there are moderate hydroureter and hydronephrosis on both sides. A small piece for micrometric examination has been taken from the ileum bladder.

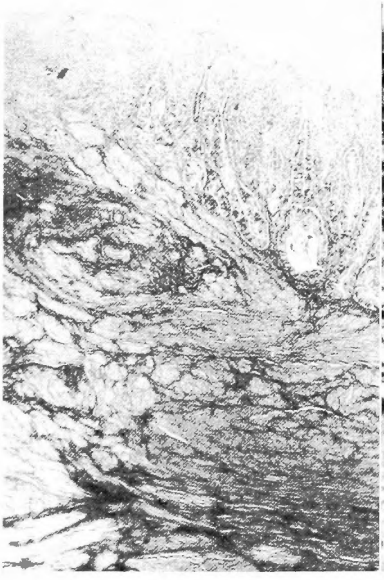
Group-C. In this group, both ends of an isolated ileal segment into which both ureters had been transplanted, was closed off, to perform side-to-end ileourethrostomy, following total cystectomy in which the urethral spincter was included (Fig. 12).

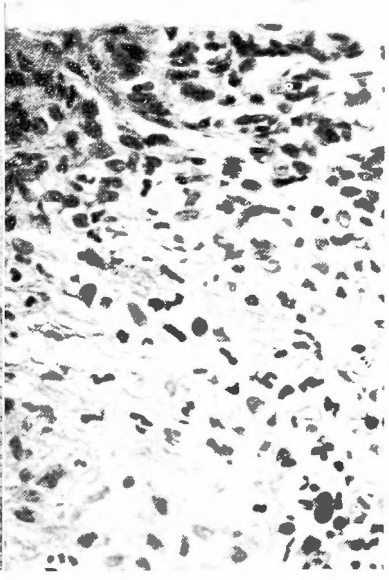
12. Dog C_1, female, 8.2 kg of body weight. The dog was operated on September 13, 1956, after the procedure mentioned above. An isolated ileal segment of 10 cm in length and 16 cc in capacity was used, and ureteroileostomy was performed by full-thickness end-to-side anastomosis. On 2nd postoperative day, the dog was not awaken from anesthesia yet, and could neither stand up, nor walk, dying on the following day. Postmortem examination revealed that the dog had been suffered from filariasis on atria cordis.

13. Dog C_2, female, 9.5 kg of body weight. Operated on October 23, 1956. A U-shaped artificial bladder was constructed according to the procedure noted above. An isolated ileal segment of 18 cm in length and 35 cc in capacity was used and ureteroileostomy was performed by full-thickness end-to-side anastomosis, the indwelt catheter being removed on 3rd postoperative day. At the end of lst postoperative week, the animal's urination became continent. But in 3rd postoperative week, the dog suffered from infectious disease and died on 20th postoperative day. At autopsy, the ileum bladder was dilated slightly and contained a moderate amount of mucus. Ureteral orifices had no stenosis. The right renal pelvis was slightly dilated and contained retrograded mucus. At microscopic examination, the sites of uretero-and urethroileostomies were completed primarily and were lined with transitional epithelium. The ileum bladder wall showed no remarkable change. The left kidney was normal; the right one had severe inflammatory lesions.

A

B





C

Fig. 9. A. anastomosis between bladder-neck and ileum. The site of anastomosis is smooth and indistinguishable; both muscle layers are connected closely. Ileal mucosa has overgrown beyond the juction of anastomosis towards the urethra, with chronic inflammation (Van Gieson stain, ×10). B: enlargement of A. Ileal mucosa is observed directly above the muscle layer of the bladder-neck (Van Gieson stain, ×30). C: the mucosa of the bladder-neck shows marked cell infiltration (Hematoxylin-eosin stain, ×400).

14. Dog C_3, female, 10.5 kg of body weight. On October 11, 1956, the operation carried out to construct a U-shaped artificial bladder. In this case, an isolated ileal segment of 16 cm in length and 26 cc in capacity was used, and ureteroileostomy was performed by full-thickness end-to-side anastomosis. On 4th postoperative day, the dog's urination became continent. At the end of 2nd postoperative week, an excetory urogram demonstrated that the right renal pelvis did not appear, but the left one showed slight hydronephrosis. At the end of 3rd postoperative week, the bladder capacity increased to 48 cc voiding 30 cc urine voluntarily. Since 4th postoperative week, the dog began to discharge eye wax, and became emaciated gradually and died on 31st postoperative day. The cause of death was supposed to be distemper. At autopsy, the ileum bladder was moderately dilated and its lumen contained a

Fig. 10. Site of ureteroileostomy. Ureteral orifice is quite patent and flush with the ileal mucosa. Site of ureteroileostomy is smoothly united with minimum fibrosis and its luminal surface is lined with ileal mucosa. Ureteral wall shows remarkable thickening (VAN GIESON stain, ×10).

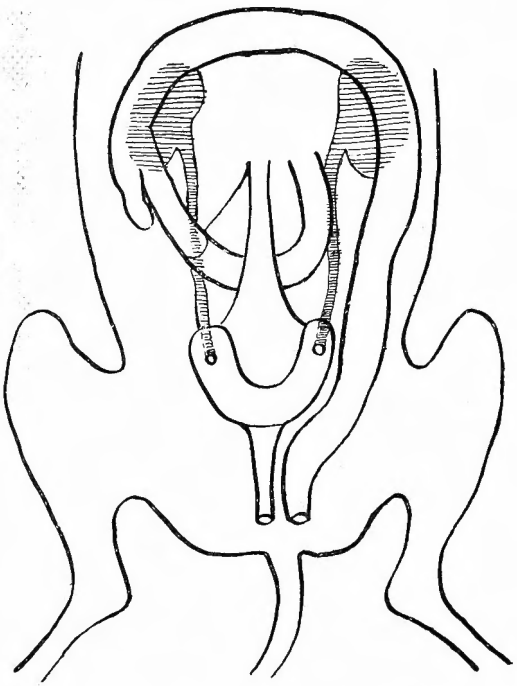


Fig. 12. U-shaped ileum bladder performed on group-C.

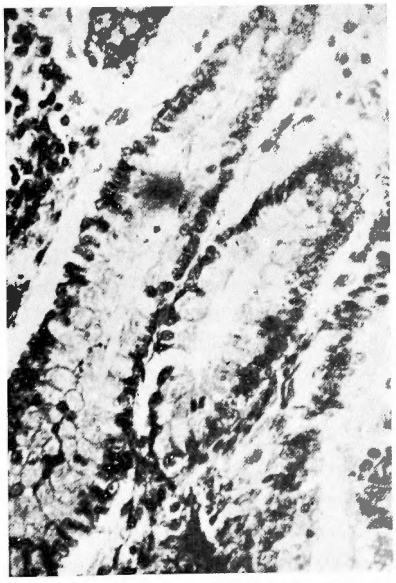


Fig. 11. Mucosa of the ileum bladder presents a picture of normal ileal mucosa, and epithelial cells of the mucosa show active secretory activity (Mucicarmin stain, ×400).

moderate amount of mucus. Ureteral orifices showed no stenosis, but a ureteral catheter remained in the right ureter, and the renal pelvis on the same side was dilated slightly. Both renal pelves contained mucus.

Microscopically, the sites of uretero-and urethro-ileostomiess howed primary healing, and mucosa of the ileum bladder showed no change. The right kidney had wide belt-shaped inflammatory lesions including medulla and cortex. The left kidney was normal.

15. Dog C_4, female, 8.5 kg of body weight. On September 14, 1956, the usual operative procedure was carried out to construct a U-shaped artificial bladder. In this case, an isolated ileal segment of 15cm in length and 28 cc in capacity was used, and end-to-side ureteroileostomy was performed, without urterourethral catheter. Since the very lst postoperative day, the dog's urination was continent, and the postoperative course was very satisfactory. An excretory urogram at the end of lst month did not show any sign of hydronephrosis. At the end of 3rd month,

the bladder capacity increased to 142 cc, while the residual urine was 12 cc. Blood chloride and nonprotein nitrogen were 385 mg dl and 36 mg dl respectively, but they maintained postoperatively the level of 400 mg to 440 mg/dl and 40 mg to 50 mg/dl respectively. On 98th postoperative day, the dog was sacrificed.

Autopsy findings: the small intestine adhered to both ends of ileum bladder. The diameter of the ileum bladder enlarged twice as large as the terminal ileum, with thickened wall. The lumen of the ileum bladder contained a moderate amount of mucus, showing smooth sites of uretero-and urethro-ileostomies. The ureteral orifices were patent and without hydronephrosis on both sides (Fig. 13). Renal pelves contained no mucus.

Fig. 13. Dog C_4. Autopsy specimen. U-shaped ileum bladder is enlarged twice as large as the terminal ileum. Arrows indicate the ureteral orifices, which are patent, and as the result, neither side shows any sign of hydronephrosis.

Fig. 14. Site of ileourethrostomy. Both muscle layers are united without fibrosis and its luminal surface is lined with ileal mucosa (Hematoxylin-eosin stain, ×10).

Microscopic findings: at the sites of uretero-and urethroileostomies, both muscle layers were united without fibrosis respectively. The sites of anastomoses were lined with ileal mucosa (Fig. 14). Muscle layers of the ileum bladder were thickened, without any change of mucosa. Concerning kidneys, there was no evidence of renal infection.

Micrometry of muscle fibers of the ileum bladder was performed, resulting in the longest of them 516μ, the shortest 359μ, the widest 13μ, and the narrowest 6μ; the mean value 408.4μ in length and 9.0μ in width. In the control, the longest was 434μ, the shortest 196μ, the widest 11μ, and the narrowest 3.5μ; the mean value 317.4μ in length and 7.4μ in width. Accordingly muscle fibers of the ileum bladder are 1.28 times as long, and 1.21 times as wide, as the control.

II. Regeneration of the Bladder.

Fourteen female dogs were used for the experiment. Eight died of surgery, within 3 postoperative weeks (R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8) Three died of pyelonephritis, respectively on 32nd, 36th, and 41st postoperative day (R_9, R_{10} and R_{11}), and only 3 survived for

complate evaluation. These 3 dogs were sacrificed on 60th, 120th, and 395th postoperative day respectively (R_{12}, R_{13} and R_{14}).

In Dog R_1 to R_{18}, a mold was inserted following total cystectomy, in which the urethral sphincter was included. As the result, urine flowed out of the catheter continuously, while the mold was indwelt, but the dogs took frequently a usual pose of urination and a few drops of urine were forced out by abdominal pressure every time. And after removal of the mold, though their urination remained incontinent, they voided still frequently a small amount of urine in a usual fashion.

Representative Cases

1. Dog R_1, female, 12.7 kg of body weight. After total cystectomy a resin mold of 35 cc in volume was inserted and indwelt on December 5, 1955. The dog could not recover from surgery, and died on 7th postoperative day.

At autopsy, the abdominal cavity was filled with a great amount of urine, and the left ureteral catheter had perforated renal pelvis. The mold was closely wrapped up with fatty tissue of 1 cm in thickness. Inner layer of the fatty tissue seemed whitish grey and fine, and its luminal surface was covered with whitish yellow slime. The mold could be easily separated from the wall. There was a small quantity of turbid whitish yellow secretion between the regenerated bladder wall and the outer surface of the mold. The capacity of the regenerated bladder was equal to the volume of the mold. The junctions of the ureters and the urethra, to the regenerated bladder united sufficiently, and ureteral orifices protruded a little, presenting slight stenosis. There was, however, neither hydroureter, nor hydronephrosis.

Microscopic findings: the innermost layer of the regenerated bladder wall was a thick inflammatory membrane consisted of numerous granulocytes, erythrocytes and fibrin combining them together. The middle layer was a young proliferating zone of fibroblastic giant cells and fibroblasts, with numerous blood capillaries. The outer layer consisted of the fatty tissue. At the junction of the regenerated bladder to the right ureter, ureteral adventitia was closely united with granulation of the regenerated bladder. The junction of the urethra to the regenerated bladder was also smoothly united. The transitional epithelium of the urethra merly showed tendency to overgrow towards the regenerated bladder.

2. Dog R_7, female, 13.5 kg of body weight. After total cystectomy, a resin mold of 35 cc in volume was inserted and indwelt on December 23, 1955. General condition of the dog was favorable postoperatively, but since 2nd week, vomiting and anorexia were recognized. On 21st rostoperative day, the dog died of intestinal obstruction.

At autopsy, the ileal loops adhered to each other, kinking to cause obstruction. The regenerated bladder wall was 0.7 to 1 cm in thickness and its luminal surface was smooth and glistening. The junctions of the bilateral ureters and the urethra, to the bladder wall were smooth and indistinguishable. The lumen of ureteral catheter has a moderate amount of urinary precipitate, but there was no sign of hydronephrosis.

Microscopic findings: the regenerated bladder wall consisted of the following 4 layers: (1) the innermost layer of concentrated dirty inflammatory membrane, (2) fibroblastic layer accompanied with round cell infiltration and numerous blood capillaries, (3) layer of fine mature fibrous connective tissue, and (4) layer of the thick fatty tissue at the outermost (Fig. 15). The junction between the urethra and the regenerated bladder was united quite smoothly. Urethral and ureteral epithelium showed a tendency to overgrow towards the regenerated bladder wall.

3. Dog R_{10}, female, 8 kg of body weight. On May 10, 1956, a polyvinyl formal mold of 13 cc in volume was inserted and indwelt following total cystectomy. Two weeks later, the dog recovered almost to the preoperative condition, so that the mold was removed and

ureterourethral catheter was inserted in its place on 15th postoperative day. Thereafter, a urinary fistula was developed in the operation scar, which closed spontaneously in the lapse of time of a few days. After the second operation, the dog remained with incontinent urination, but often took a usual pose, voiding each time a small amount of urine. Since 4th postoperative week, urine became turbid and anorexia followed. The dog became markedly emaciated and ultimately, died on 36th postoperative day.

Autopsy findings: the regenerated bladder adhered widely to the uterus and the anterior abdominal wall. The regenerated bladder wall was 0.8 cm in thickness and its luminal surface was smooth and glistening. The junction between the urethra and the regenerated bladder was smooth and indistinguishable. Ureteral orifices showed marked stricture. There were hydroureter and hydronephrosis, highly on the right side and moderately on the left. Dilated renal pelves were filled with turbid urine.

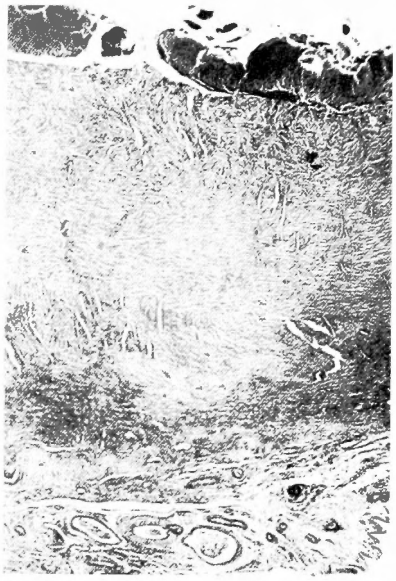


Fig. 15. Wall of the regenerated bladder. It consists of 4 layers: the innermost layer of inflammatory membrane, a fibroblastic layer, a layer of mature fibrous connective tissue, and a layer of fatty tissue at the outermost (Hematoxylin-eosin, × 15).

Microscopic findings: inflammatory membrane which had covered the inside of regenerated bladder was replaced by fibroblastic layer accompanied with cell infiltration and numerous blood capillaries and fibrin mass attached here and there on the surface. A thick wall of fine fibrous connective tissue was already established on the outside of the layer. The junctions of the ureters and the urethra to the regenerated bladder was completely united, and transitional epithelium of the ureter and the urethra overgrew to the luminal surface of the bladder, but it had not lined up the surface completely. Both kidneys contained wide spread inflammatory lesions with cell infiltration and destruction of the tissue.

4. Dog R_{12}, female, 10 kg of body weight. On January 23, 1957, a polyvinyl formal mold of 15 cc in volume was inserted and indwelt following total cystectomy. Postoperative course was very favorable. On 3rd postoperative day, blood chloride was 443 mg dl and nonprotein nitrogen 61 mg dl; and at the end of lst week, they decreased to 390 mg dl and 39 mg dl respectively. At the end of 4th week, the second operation was performed, the mold was removed and the ureterourethral catheter was inserted in its place. But the catheter fell off three days later. Since then the dog became slightly incontinent, and taking the usual pose, frepuently voided several cc of urine each time. After the second operation, the dog used to have 400 mg dl of blood chloride and 50 mg dl of nonprotein nitrogen, and was quite healthy. At last it was sacrificed on 60th postoperative day.

Autopsy findings: in the abdominal cavity, there was no remarkable change. The regenerated bladder firmly adhered to the anterior abdominal wall and the uterus. Its capacity was 12 cc and rather smaller than the volume of the mold. The wall was 0.7 cm in thickness, and consisted of the outer fatty tissue and the inner fine mature granulation layer; both layers could be separated easily. The luminal surface of the bladder was smooth and glistening; and the joining part to the urethra was indistinguishable. Ureteral orifices showed slight stenosis,

but were sufficiently patent and flush with the luminal surface of the regenerated bladder. There was a bone-like tissue of about 0.5 cm in diameter, underneath the surface between both ureteral orifices. The renal pelves on both sides were dilated moderately, but urine stagnated there, was clean (Fig. 16).

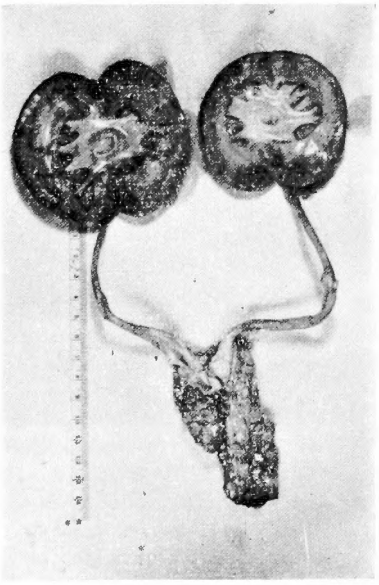


Fig. 16. Dog B_{12}. Autopsy specimen. Luminal surface of the regenerated bladder is smooth and glistening. Ureteral orifices come close to each other and show slight stenosis. Both kidneys show moderate hydronephrosis.

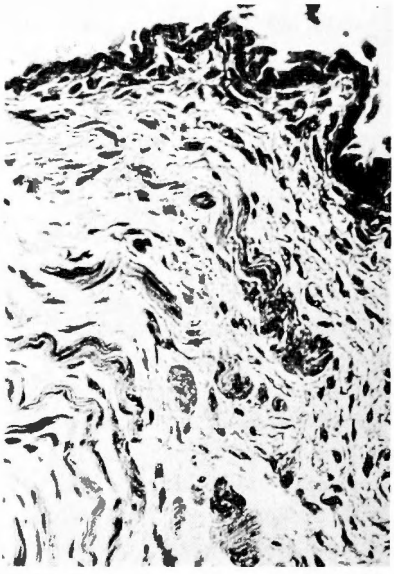


Fig. 17. Wall of the regenerated bladder, It consists of (1) several layers of uroepithelial cells, lining the luminal surface, (2) a thin layer of fiibroblast, and (3) a thick layer of mature fibrous connective tissue including numerous bundles of smooth muscle fibers (Hematoxylin-eosin stain, ×400).

Microscopic findings: the regenerated bladder wall consisted of (1) several layers of uroepithelial cells, lining the luminal surface, (2) a thin layer of fibroblast with many blood capillaries, (3) a thick layer of mature fibrous connective tissue including many bundles of smooth muscle fibers, and (4) outermost thick fatty tissue (Fig. 17). The junction of the urethra and the regenerated bladder wall was smoothly united. At the joining point of the ureter to the regenerated bladder, there was no proliferation of connective tissue. Transitional epithelium of the urethra and the ureter overgrew towards the regenerated bladder and lined the luminal surface completely. A thin bone-tissue grew newly and directly underneath the uroepithelium. Both kidneys showed no sign of acute infection.

5. Dog R_{13}, female, 14 kg of body weight. On November 27, 1956, a polyvinyl formal mold of 15 cc in volume was inserted and indwelt following total cystectomy. The postoperative course was favorable. On 30th day, the mold was removed and the ureterourethral catheter inserted in its place. The catheter was found to have fallen off after 3 days. Since then the dog's urination was incontinent, but the incontinence improved gradually in the lapse of time of a month after the second operation, voiding voluntarily about 10 cc of urine. Though blood chloride and nonprotein nitrogen showed temporal increase after the first and the second operation, they maintained, on the whole, a level slightly higher than that of preoperative value. The dog was quite healthy till sacrificed on 120th postoperative day.

Autopsy findings: there was no remarkable change in the abdominal cavity. The regenerated bladder adhered firmly to the anterior abdominal wall and the uterus. It contracted remarkably and its capacity was only several cc. The wall of the regenerated bladder was 1.2 cm in thickness and luminal surface was smooth and glistening. The junction between the urethra and the regenerated bladder was in distinguishable. Both ureteral orifices came close to each other, and a hard bone-like tissue was palpated in the area of about 1 cm in diameter including these orifices, which showed slight stenosis, with also slight hydronephrosis on both sides.

Microscopic findings: the regenerated bladder wall was of the same construction as that of Dog R_{12}, but the layer of fibrous connective tissue fairly thickened in comparison with that of Dog R_{12}. Subepithelial zone showed marked cell infiltration. It was recognized that a thin bony tissue had been formed underneath the epithelium around the ureteral orifices in accordance with palpation (Fig. 18). Both kidneys were normal.

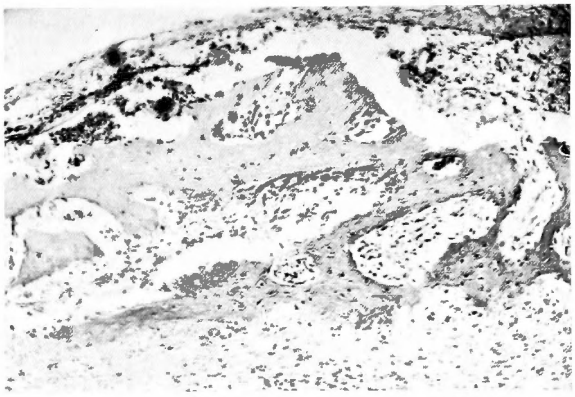


Fig. 18. Ossifiication at the dome of the regenerated bladder. Thin bony tissue is recognized underneath epithelium (Van Gieson sain, ×100).

Fig. 19. Dog R_{15}. Autopsy specimen. Lower half of the regenerated bladder consists of the dilated original bladder neck, and upper half of the regenerated part. Both ureters and pelves show marked dilatation especially, right kidney shows a hydronephrotic contracted one.

6. Dog R_{14}, female, 10 kg of body weight. On February 23, 1956, a polyvinyl formal mold of 25 cc in volume was inserted and indwelt following cystectomy, in which a very small portion of bladder neck was preserved. The dog recovered completely at the end of lst postoperative week, and since the end of 2nd week began to lose appetite and became slightly emaciated; blood chloride and nonprotein nitrogen increased to 410 mg/dl, 47 mg/dl respectively. Accordingly on 19th postoperative day, the mold was removed and a ureterourethral catheter was inserted in its place. The wall of the regenerated bladder was 1 cm in thickness with smooth luminal surface; urinary flow out of ureteral orifices was also noticed. On 7th day after the second operation, the catheter was removed, which was followed by gradual decrease of blood chloride and nonprotein nitrogen. The dog got on favorably, even though with incontinent urination. At the end of 3rd month, she was still incontinent partially, but voided voluntarily 20 to 30 cc of urine at the interval of about 30 minutes, maintaining about 400 mg dl of blood chloride and 40 to 50 mg dl of nonprotein nitrogen. The dog became perfectly continent at the end of 9th postoperative month and came

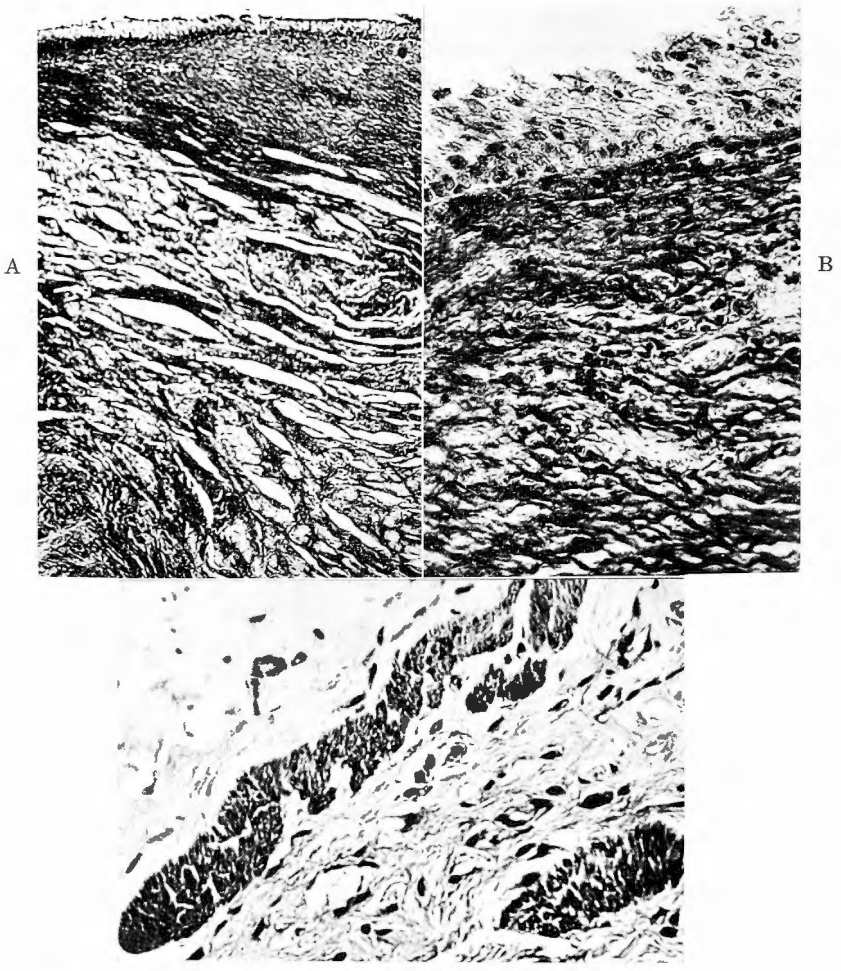
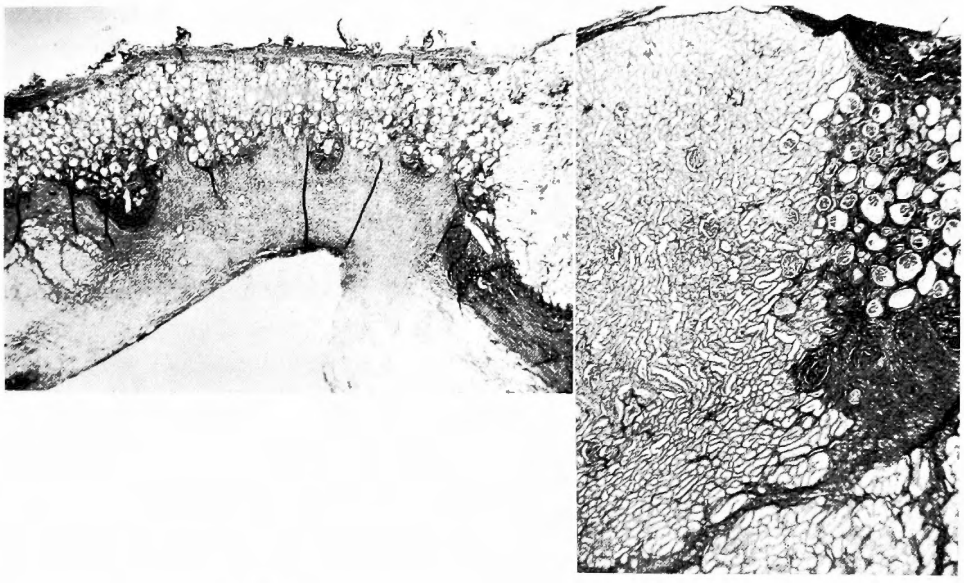


Fig. 20. Wall of the regenerated bladder. A: the wall consists of (1) several layers of transitional epithelial cells lining the luminal surface, (2) a thin layer of fine fibrous connective tissue, (3) a thick layer of mature fibrous connective tissue including many bundles of smooth muscle fibers (Van Gieson stain, ×50). B: enlargement of A. Uroepithelium is seen above fine fibrous connective tissue (Van Gieson stain, ×400). C. demonstrates bundles of the smooth muscle in the regenerated bladder wall (Hematoxylin-eosin stain, ×400).

to be able to void voluntarily about 40 cc of urine at the interval of 40 to 60 minutes. An excretory urogram at the end of 12th month demonstrated marked dilatation of the ureters and the pelves and a cystogram showed ureterorenal reflux. The capacity of the reconstructed bladder was 50 cc. The dog was sacrificed on 395th postoperative day, though she was quite healthy.

Autopsy findings: there was no marked change in the abdominal cavity and the regenerated bladder with 50 cc capacity adhered slightly to the uterus and the anterior abdominal wall. When the lumen was opened, a urinary stone of small finger tip size was found. The wall of the newly constructed bladder was 1 cm in thickness and there was no fatty tissue. The lower half consisted of the dilated neck of the original bladder, and the upper half of the regenerated part, both halves uniting each other smoothly. There was a hard bone-like tissue



A B

Fig. 21. A: the right kidney shows a picture of hydronephrotic contracted kidney (VAN GIESON stain, ×10). B: the left kidney. A few cicatrized lesions are scattered in the normal renal tissue (VAN GIESON stain, ×50).

on the area of about 1 cm in diameter near both ureteral orifices. Ureteral stomata showed slight stenosis, but were flush with the luminal surface of the regenerated bladder. Both ureters dilated markedly with the thickened wall. The kidneys presented lobular shape, and the renal parenchyma contracted and became thin; the renal pelves dilated to a great extent, especially on the right side (Fig. 19).

Microscopic findings: the regenerated bladder wall consisted of (1) several layers of transitional epithelial cells lining the luminal surface, (2) a thin layer of fine fibrous connective tissue, (3) a layer of thick mature fibrous connective tissue including numerous bundles of smooth muscle fibers, and (4) the outermost layer of the scanty fatty tissue (Fig. 20). The regenerated bladder wall was smoothly connected with the remaining bladder neck and the ureter. Transitional epithelium of the original urinary tract overgrew and covered the regenerated bladder completely.

The right kidney showed a picture of hydronephrotic contracted kidney, that is, calices were dilated highly and renal parenchyma became markedly thin. In the parenchyma, disappearance of tubules, various sized glomeruli, and marked proliferation of interstitial connective tissue were observed over the wide area of the kidney. On the left kidney, these changes were slight in their extent. Neither of kidneys showed signs of acute infection (Fig. 21).

DISCUSSION

I. Ileum Bladder.

BISGARD, RUBIN, and THOMPSON substituted a segment of sigmoid for the urinary bladder of dogs with the same purpose as mine. All of them maintained urinary continence with the urethral sphincter this corresponds to group-B of my experiment. But in many cases of malignant diseases of the bladder, a portion of

the urethra (prostate in case of a male) should be resected together with the bladder. In case of exstrophy of the bladder, which is one of benign diseases and to which this operative procedure should be applied, the urethra can not be utilized because of the open exteriorized urethra. Accordingly, the application of this operative procedure in these cases would inevitably be accompanied by incontinence. Group-A of my experiment proved this fact. All the dogs of group-A in which a substitute ileum bladder was constructed following total cystectomy including the urethral sphincter showed partial urinary incontinence all through their postoperative course. This permanent incontinence was of much influence upon the postoperative condition of the test animals. In 2 cases of this group, ulceration developed in the perineal region caused by contamination with urine. In cases of group-B, where urethral sphincter was utilized for maintaining urinary continence, as BISGARD, RUBIN, and THOMPSON did, the dogs became continent immediately or a few days later, after removal of the catheter. The long survived dogs of 165 days and 311 days (B_1 and B_3) were quite satisfactory regarding urinary continence, and were well controlled. But the range of its application is much limited. In cases of group-C, where a U-shaped substitute ileum bladder was constructed following total cystectomy including the urethral sphincter, all the dogs were continent in urination postoperatively. That is, a dog without ureterourethral catheter became continent on the very next day of the operation. The other cases became continent 2 to 4 days after removal of the catheter. It has been proved in this method that urinary continence can be mainlained even in cases where urethral sphincter is not preserved.

This is a striking fact. Then, why could continence be maintained in the dogs without urethral sphincter? As is mentioned above, the side-to-end ileourethrostomy was performed in group-C, so that urine in the segment will probably, owing to natural peristalsis of the segment itself, flow along the longitudinal direction beyond the urethral orifice opened at the lateral side of the segment, and be pooled in the distal end of the segment presenting a blind pouch. When the inner pressure of the segment has reached a certain degree, then urine may be voided through the stoma to the urethra. Such a biodynamic mechanism will, as the matter of course, disturb the natural flow of urine, more than in cases of other groups. It is indeed possible to say that the phenomenon of periodical urination in group-C is functional continence, but I should like to consider that it is nothing but the urethral flow disturbed, or a special form of incontinence.

Ureteroileostomy: Three methods were performed in my experiment - COFFEY's submucosal tunneling method, KERR and COLBY's method and full-thickness end-to-side ureteroenterostomy. KERR and COLBY's method is, as it were, COFFEY's method without submucosal tunneling: these two methods belong to pull-through ureteroenterostomy. The postmortem examination of the dogs which underwent this pull-through method showed, in all cases, formation of either a rosette or a nodule at the ureteral orifice, which was the very place where stenosis used to occur in a whole course of ureter. Especially Dog A_1 (13 days), A_2 (29 days), and B_1 (35

days) showed marked stenosis accompanied by pyohydronephrosis, at the ureteral orifices.

On the contrary, in 10 dogs which underwent the full-thickness end-to-side ureteroileostomy, postmortem examination revealed that the ureteral orifices were quite patent and flush with the intestinal mucosa, without formation of neither rosette nor stenosis owing to cicatrization. By means of this full-thickness method, I could obtain long survival cases of 82 days (A_5), 98 days (C_4), 165 days (B_5), and 311 days (B_8), in group-A, -B and -C.

Microscopically, at the end of 2nd postoperative week, the site of the anastomosis showed primary healing and its luminal surface was lined with uroepithelium. In cases of the long survived of more than 2 months, proliferation of the fibrous connective tissue at the site of anastomosis was very slight and muscle layer of both the ureter and the ileal segment were united. In this method, interposition of connective tissue between the cut surface of the ureter and the bowel is checked to minimum, because the site of anastomosis is rapidly lined with uroepithelium as CHAPUT, CORDONNIER and MALUF reported previously.

In some dogs of the long survival cases which were treated with this full-thickness method, the postmortem examination showed formation of moderate hydronephrosis and hydroureter, and regurgitation of mucus of the ileal segment to the renal pelvis. The prime function of the anastomosis, however, is to procure patency of ureteral orifices to provide adequate drainage. Regurgitation, therefore, is potentially possible. I believe that it is impossible to prevent ureterorenal reflux due to parsistently incerasing pressure in the artificial ileum bladder, whichever existing method of transplanting ureter may be used. Therefore the full-thickness method is better than the pull-through method because of that (1) there is not any danger of either stenosis or obstruction of ureteral orifices, (2) the subsequent destructive renal infection is able to be avoided, and (3) it is convenient in postoperative instrumentation.

What we should do at present when there is no ideal anastomosis method capable of preventing stenosis and reflux satisfactorily, is to make effort to avoid, as much as possible, acute and recurrent infection due to stenosis and reflux lest fatal renal insufficiency should be developed.

BISGARD formed experimentally a sigmoid bladder in a 2 stage procedure. At the first stage, a colostomy was performed at the proximal stump of the sigmoid. The distal end was closed off and the right ureter was implanted therein by COFFEY's method. At the second stage, 14 days later, the left ureter was implanted, the bladder extirpated and the segment of sigmoid isolated and anastomosed to the urethra. It can be considered that it enables to maintain a constant passage of urine at least on one side, and at the same time plays an important part in purifying the intestinal loop as a substitute bladder.

The following conclusion, however, can be drawn out of my experiment: when transplantation of the ureter is performed by the direct mucosa-to-mucosa method and such powerful intestinal antiseptics like neomycin and others are administered

effetively, a satisfactory substitute bladder can be successfully constructed in one stage procedure.

Ascending Renal Infection: In this experiment neither chemotherapeutics nor antibiotics were administered against possible renal infection through postoperative course. As the result, in seven cases out of 13 in which autopsy examination was performed, the kidney revealed microscopically the evidence of renal infection on either one or both sides.

Three dogs underwent pull-through ureteroileostomy and all of them had marked stenosis of the ureteral orifices being accompanied by pyohydronephrosis in comparatively early stage of 13th to 35th postoperative day. In one case, the right ureteral catheter was sutured by mistake in ureteroileostomy, so that the catheter remained till 32nd postoperative day; the lumen was occluded with urinary precipitate, which was accompanied by pyelonephritis only on the same side. In these advanced renal infection owing to marked stenosis of the ureteral orifices, the histologic section of the kidney presented wide inflammatory lesion with remarkable tissue destruction.

In the other 3 cases in which ureteral passage had been established, ascending renal infection presented, in general, lesions comparatively localized and radiately scattered including medulla and cortex, as follows: (1) Some tubules of the lesions were packed up with mass of leucocytes, chiefly in the medulla; epithelial cells of tubules degenerated, dissociated, or disappeared. (2) There was marked interstitial cell-infiltration, which, in some cases, developed subsequently into small abscess. (3) No marked change was noticed in glomeruli. (4) These inflammatory changes were more remarkable around medulla than around cortex. In two of these three cases a greater part of the renal parenchyma was normal, and there were such scattered lesions as mentioned above, and cicatrized old ones: these changes suggested repetition of mild ascending renal infection due to contamination of the newly reconstructed bladder and ureteral reflux. In one of these three cases, there was mild infection only in the kidney on one side, where the ureter was anastomosed to an antiperistaltic loop of the ileal segment used as a U-shaped substitute bladder. Therefore, so far as infection is concerned, it may be rational to perform ileoureterostomy isoperistaltically rather than antiperistaltically.

Goldstein, Hinman and Weyrauch pointed out, ascending infection is related to the degree of contamination at the place where the ureter is introduced. Concerning the route of infection, David and Mattil advocated that infection would spread to the renal pelvis chiefly through the ureteral lumen rather than through periureteral lymphatics. Thompson cultivated urine from 5 long survived dogs with sigmoid bladder, and reported that infection was detected in all cases. Rubin also reported positive growth of bacterial culture of catheterized urine of dog with sigmoid bladder in 7 postoperative months, concluding that there was always mild infection in the new bladder, but it was controlled with antibiotics without ascending infection to the upper urinary tract. In these reports, however, there was no description of microscopic investigation. At any rate it is proper to consider that

bacterial infection of the substitute bladder always exists because secretion of mucus from the intestinal loop wall used as the substitute bladder is still active postoperatively. This fact suggests the constant existence of a danger of ascending infection. In some of my long survived cases, repetition of mild renal infection was proved microscopically, and at the same time ureteritis was noticed.

Ascending renal infection recognized in my experiment can be roughly divided into the following two types: (1) destructive renal infection owing to ureteral obstruction in comparatively early stage and (2) repeated mild infection in the long survived cases. I believe that the former should be perfectly prevented by end-to-side ureteroenterostomy and the latter be controlled satisfactorily by appropriate use of antibiotics.

Changes of the Isolated Ileal Segment: Capacity of the ileal segment used as a substitute bladder increases gradually in proportion to the lapse of postoperative days. For example, the ileum bladder of dog B_6 which was continent in urination, showed 270 cc capacity of the bladder in 8th month, that is, the capacity has inceased ten or more times as large as that at the operation, but expelling power of urine by voluntary urination was yet weak, taking more time than normal dog. And there was residual urine mixed with a moderate amount of mucus. One of the reasons for this fact may consist in performing antiperistaltic ileourethrostomy. Thompson and Rubin also reported that the substitute bladder was enlarged about ten times as lrage as the original one in several postoperative months. Bisgard reported also that the female dog with sigmoid bladder squatted to urinate, but the male dog was usually unable to expell urine forcibly when he took a usual pose toward trees or posts. In cystography of my long survived cases, the substitute bladder showed normal ileal movement.

The wall of ileal segment in these long survived cases thickened to 1.5 times as thick in ten months, as that of the terminal ileum of the same dog. Micrometric examination of smooth muscles of the ileum bladder wall showed that muscle fibers had hypertrophied the length by 1.3 times, width by 1.2 times in 3 months (C_4), the length by 1.8 times and width by 1.7 times in ten months (B_6). Higgins said in the discussion attached to the report by Rubin, "I performed a permanent colostomy on a series of dogs, and utilized the lower segment of the rectosigmoid as a bladder after transplanting the ureters into this part of the bowel. For over a year every thing was satisfactory, but at the end of 2 years this segment of bowel contracted down so its cpacity was practically nil. Whether this was interference with the nerve supply or absence of fecal content in the bowel, I do not know." This suggests that there is a limit in compensated hypertrophy of the intestinal wall muscle and that a great deal of care is to be taken lest the substitute intestinal bladder should be overloaded without intervals.

As for mucosa of the ileum bladder, none of the cases showed marked change; it presented a picture of normal ileal mucosa, and had a good many goblet cells, and its secretory function was still active even after 10 postoperative months. Merricks implanted the ureters into the isolated cecum and utilized the appendix

as a fistula, to enable the patient to live 15 years. He noticed in autopsy that mucosa of the cecum had lost glandular elements and resembled the normal urinary bladder. BISGARD, CARR, and RUBIN, however, reported that mucosa of the sigmoid bladder of the dog showed a normal colonic histologic picture after 2 postoperative years.

Therefore, so long as an isolated intestinal segment has sufficient blood supply, neither metaplasia of mucosa nor overgrowth of uroepithelium towards the intestinal segment is to be expected. As a matter of fact, on the contrary to this expectation, I have often found that mucosa of the ileal segment had overgrown beyond the anastomotic scar towards the ureters and the urethra, with chronic inflammation; the new bladder made of bowel has naturally stronger resistance against infection than the ureter or the urethra, that is, it might be that both the ureter and the urethra had been affected by some germs, which could not cause any inflammatory change in the new bladder.

Some Suggestions for Future: (1) An isolated ileal segment should be washed sufficiently, and sterilized with intestinal antiseptics prior to the operation. (2) In clinical application, full-thickness method may be used to perform ureteroileostomy. (3) In case that the urethral spincter can be utilized, end-to-end ileourethrostomy should be performed isoperistaltically. If it can not be utilized, both ends of the isolated ileal segment should be closed and side-to-end ileourethrostomy should be performed to form an L-shaped ileum bladder. (4) In suturing, chromic catgut should be used. (5) Determination of blood electrolytes and nonprotein nitrogen, and bacteriological examination of urine should be done periodically after the operation. (6) Chemotherapeutics and antibiotics should be properly administered as occasion demands. (7) The substitute bladder should be irrigated periodically and the patient should be taught to void urine regularly. It is desirable to lighten a burden of the new bladder by continuous catheterization by night.

Following the suggestions mentioned above, an artificial bladder made of ileal segment may be constructed successfully, but there are still a few factors to be investigated further, for example, ureterorenal reflux, ascending renal infection etc. I should like to concentrate all my efforts in future to find some solutions of these problems.

II. Regeneration of the Bladder.

The operative procedure of this experiment consisted of 2 stages; in the first stage, cystectomy and insertion of a mold were performed, and in the second stage, the mold was removed. After the first stage operation, many dogs died, in the early postoperative period, of fatal complications owing to instability of the fixation of a resin mold to the ureters and the urethra. On the contrary, in case treated with a polyvinyl formal mold such dangers could be reduced, as the mold was spongy and flexiable, and the ureters and the urethra could be sutured and fixed to the mold itself. Volume of the mold had to be considered in proportion to the weight of the animal and development of perivesical fatty tissue, but that of 20 to 30 cc in volume was most suitable.

Decision of the time for the second operation was rather difficult. A considerable amount of precipitate of urinary elements was already recognized in the lumen of ureteral cathcters attached to the mold, within 3 postoperative weeks, where the catheters should be cleared with stylet to prevent obstruction, but it was difficult in case of experimental animals. Therefore the mold was left indwelt untill appearance of symptoms of uremia, such as anorexia and vomiting. But as granulation of the regenerated bladder was not sufficiently mature within 3 postoperative weeks, it sometimes caused marked contraction of the regenerted bladder or stricture of the ureteral orifices, to remove the mold in this period. Accordingly, it is ideal to remove the mold in 5 to 8 postoperative weeks when granulation layer is expected to be mature.

Therefore it was very difficult to enable the animal to survive for a long term in this experiment. Seven dogs died of complications before the removal of the mold and four dogs died of complications after its removal.

Complications before the Removal of the Mold: Dog R_1 and R_3 died of intraabdominal urinary leakage owing to perforation of the renal pelvis by ureteral catheter and falling of the ureter, on 7th and 11th postoperative day respectively. Dog R_2, R_4 and R_5 died of panperitonitis owing to spread of inflammation of the regenerated bladder into the abdominal cavity, on 8th, 15th and 16th postoperative day respectively. Dog R_7 died of intestinal obstruction owing to postoperative intestinal adhesion, on 21st postoperative day. In these dogs died within 3 weeks, there was neither sign of hydronephrosis grossly, nor ascending renal infection microscopically. Blood chloride and nonprotein nitrogen reached maximum on 4th to 7th postoperative day, similarly to the case of the ileum bladder, and decreased to the level a little higher than the preoperative value, on 10th to 14th postoperative day, maintaing that level thereafter. In dog R_{11} which the mold had been inserted for 7 weeks, blood chloride and nonprotein nitrogen began to increase again since 4th postoperative week, showing symptoms of uremia; the dog died at the end of 7th week. The autopsy examination revealed there had been an obstruction of ureteral catheters owing to precipitation of urinary elements, and subsequent pyohydronephrosis and perinephritic abscess. Therefore it is necessary to maintain patency throughout by periodical clearing of the ureteral catheters with stylet, and to administer proper urinary antiseptics effectively.

Complications after the Removal of the Mold: In cases resected the urethral spincter, the dogs showed always urinary incontinence after the second stage operation, developing temporal urinary fistula in the operation scar in almost all cases. In dog R_6, R_7, R_8, R_9 and R_{10} which underwent the second stage operation within 10 to 15 days after the first stage operation, blood chloride and nonprotein nitrogen elevated again markedly after removal of the mold; the dogs died 5 to 21 days after the second operation. Their postmortem examination revealed marked contraction of the regenerated bladder, stricture of ureteral orifices, and subsequent pyohydronephrosis. These complications are inevitable results following removal of the mold in early stadium while acute inflammation still remains, as WEYRAUCH

and HINMAN expressed; that is, ascending infection and obstruction are directly attributable to the degree of contamination of the field into which the ends of the ureters are introduced.

In my experiment, where any precautious treatment was not performed against renal infection, and excretory and retrograde urograms in some cases showed dilatation of the renal pelves with ureterorenal reflux, the experimental dogs that survived more than 2 months showed neither physical signs of renal infection, nor elevation of blood chloride and nonprotein nitrogen, and their general condition was satisfactory till they were sacrificed. Autopsy examination revealed, in all of these cases, mild stenosis of ureteral orifices, subsequent slight or marked hydronephrosis, and bone formation in a small area on the regenerated bladder wall near ureteral orifices. Furthermore, a urinary stone of small finger tip size was recognized in one case.

Microscopically, in these cases, kidneys presented cicatrized lesions of various degree, but without any evidence of acute infection. In other words, as will be described later, the danger of ascending renal infection is considered to be very scarce since 3rd postoperative month, when the luminal surface of the regenerated bladder is lined completely with the uroepithelium.

Changes of the Regenerated Bladder and the Upper Urinary Tract: I have successfully obtained long survival cases of 2 months, 4 months and 13 months, by overcoming the difficulties in the operative technique and preventing various kinds of complications, and am going to pursue changes in the regenerated bladder and upper urinary tract, on the basis of these long survival cases.

In lst to 3rd postoperative week, capacity of the regenerated bladder coincided exactly with volume of the mold. Its wall was about 1 cm in thickness, with the inner half consisted of a layer of acute inflammatory granulation. The wall consisted microscopically of (1) the innermost inflammatory membrane, (2) a fibroblastic layer, (3) a thin layer of fine fibrous connective tissue, and (4) the outermost fatty tissue. The lumen of ureteral catheters has fairly much urinary precipitate, but it was still patent and no hydronephrosis was noticed in this state. Blood nonprotein nitrogen, in a representative case, was preoperatively 34 mg/dl; on 4th postoperative day, 61 mg/dl; and on 7th day, it decreased to 39 mg/dl and maintained this level thereafter.

In 4th to 6th postoperative week, the regenerated bladder wall was about 1 cm in thickness, and its inner layer of granulation was about 0.3 cm and was clearly distinguished from the outer fatty tissue layer, being seperated from each other. The regenerated bladder wall presented microscopically a picture of chronic granulation tissue. That is, it consisted of (1) a fibroblastic layer with round cell infiltration, (2) a thick layer of mature fibrous connective tissue, and (3) the outer layer of fatty tissue. Uroepithelium showed tendency to overgrow from urethral stump to the new bladder, but it did not line the whole lumen. If urinary precipitation in a ureteral catheter is not removed, a danger of obstruction and infection in the upper urinary tract will increase; blood nonprotein nitrogen which

recovered to the preoperative level in about 10 postoperative days, showed a tendency to elevate again in many cases. It is considered that so long as the mold was indwelt, the regenerated bladder wall would have suffered mild inflammation repeatedly, without proliferation of uroepithelium, so that the mold should be removed in this stage when granulation has matured.

At the end of 2nd month, in a case where the mold had been already removed, the capacity of the regenerated bladder coincided almost with that of the mold. The wall was also 1 cm in thickness and the inner layer of granulation tissue was 0.3 cm; the inside, however, was grossly very smooth and glistening, and it could be noticed in a glance that it had been lined with epithelium. It consisted microscopically of (1) several layers of transitional epithelial cells, (2) a thin layer of fibrous connective tissue, (3) a thick layer of mature fibrous connective tissue with numerous bundles of smooth muscle fibers, and (4) the outer thick layer of fatty tissue. In this stage, formation of the regenerated bladder was morphologically completed and ossification was already noticed also in small area of the bladder wall. Blood nonprotein nitrogen showed a temporal elevation after removal of the mold, to be decreased gradually in proportion as the time elapsed, and to maintain the level a little higher than the preoperative value.

After 2 postoperative months, the regenerated bladder, as will be described later, was markedly influenced by the presence of urethral sphincter. In a case without urethral spincter (R_{13}), the regenerated bladder markedly contracted and its capacity was only several cc when the dog was sacrificed on 120th postoperative day; while in a case where the sphincter or the bladder neck was preserved (R_{14}), in 13th postoperative month, the capacity of the new bladder increased twice as much as the volume of the mold. The dog's urination was continent, and the bladder was well controlled. The bladder wall of 1cm in thickness consisted chiefly of a thick layer of mature fibrous connective tissue including many bundles of smooth muscle fibers, and the luminal surface was lined completely with uroepithelium; the outer fatty tissue layer had almost disappeared already. And so, since 3rd postoperative month, it seemed that there would be no danger of renal infection.

On the Development of Reconstructed Tissues during the Formation of the Regenerated Bladder:

1.*Granulation Tissue.* Inflammation is apt to occur at the inside of the fatty tissue enclosing the mold, due to mechanical and chemical stimulation by the mold, urine or infection. As the result, it was quite natural that formation of granulation tissue should be noticed in its healing process. It is the real fact which has been admitted since VIRCHOW that ploriferation of fibroblasts and blood capillaries should grow out of fatty tissue.

2.*Overgrowth of Transitional Epithelium.* Transitional epithelium which lines the regenerated bladder overgorws both from the urethra and the ureter. Its reproductive ability is well known; in the bladder of a dog, however, mitosis is active in the basal layer of the epithelium, while in the middle layer, amitosis is

recognized frequently. NEUHOF repaired a large defect of the bladder with free fascial graft of dogs and reported that the overgrowth of uroepithelium towards the graft could be noticed in early stadium after operation. BARET made exstrophy of the bladder in dog and after 3 weeks repaired the defect with 5×7 cm facial graft and reported that on 52nd postoperative day the graft was found to have been completely lined with the uroepithelium. SHOEMAKER, using dogs, performed subtotal cystectomy and repaired the defect of the bladder with an inverted seromuscular graft of intestine, and he noticed that the graft was lined with uroepithelium completely on 19th postoperative day. In my experiment, acute infiammatory signs of granulation layer of the regenerated bladder wall almost disappeared at end of lst postoperative month, and the overgrowth of uroepithelium was completed at the end of 2nd postoperative month. Though regenerating ability of uroepithelium is powerful as above mentioned, it is certain that there should be some factors to restrain its activity, among which infection of the reconstructed pouch is the one in my experiment. If it is possible to prevent infection effectively, the time of uroepithelium to cover the inner surface of the regenerated bladder would be shortened and, in addition, such complications as renal infection or ossification would be also minimized too, a more satisfactory regenerated bladder being formed as the result.

3. *Appearance of Smooth Muscle.* In the dogs survived more than 2 months, it was recognized that the bundles of smooth muscle fibers were also appearing in the regenerated bladder wall. BUSACHI noticed that smooth muscle had been regenerated in the scars following injuries of the prostate, the intestines and the uterus. JAKINOWITSCH showed, using animals, that new smooth muscles were proliferated by amitosis after the injuries of the lung and the stomach. BERRY, in clinical cases in which curettage of the uterus was performed, showed that the granulation tissue was repaired by active young muscle cells with a lot of pictures of mitosis. BOWDEN reported also many cases where smooth muscles were regenerated in the scar of the lung due to injuries and he supposed that regeneration of new smooth muscles was not the result of mitosis of smooth muscle which had previously exsisted there, but might be derived from the connective tissue. In my experiment, it is an actual fact that appearance of smooth muscles has been noticed in the regenerated bladder wall; but it is difficult to determine its origin.

4. *Ossification.* NEUHOF, DEMUTH and BARET repaired experimentally a large defect of the bladder with free fascial graft, and noticed ossification in the graft of some dogs. BOHNE (1955), who tried the same experiment as mine in one of the dogs which survived 9 months, recognized ossification underneath uroepithelium of the regenerated bladder.

In my experiment, in a dog sacrificed on 60th postoperative day, ossification of 1 cm in diameter was recognized at the dome of the regenerated bladder, and in another sacrificed on 120th postoperative day, that of 1 cm in diameter, including both ureteral orifices which approched each other; in one sacrificed on 395th postoperative day, 2 ossificated sites of 1 cm in diameter were found on each

lateral wall, and near each orifices respectively. Then, why does this ossification occur by transplantation of a free fascial graft or in regeneration of the bladder ? The special conditions common to these experiments are (1) that the free fascial graft has no blood supply and fatty tissue is very poor in it, too, (2) that it is granulation that plays an important part in these experiments, and (3) that granulation tissue is irrigated by a medium of urine, directly or indirectly. It is difficult to decide which of these three supposed causes has played a chief role. But at least the following facts are clear: The fibrous connective tissue and the bone-tissue have a common embryonal origin; as VIRCHOW pointed out, the granulation tissue is nothing but the connective tissue; the bone marrow is a typical one of these granulation tissues; and granulation tissue does not always generate the same tissue as the original, changing into bone-tissue according to the condition, with possible reversibility. Accordingly it can be easily understood that fibroblasts (granulation) which have played the chief role in my experiment, might change into the bone-tissue under special conditions mentioned above. I could prove in the long term survival cases that this new bone had caused no disturbance in the functional activity of the bladder. In the dog sacrificed on 120th postoperative day, the bone-tissue had surrounded ureteral orifices on both sides, but stenosis there was slighter than that of the other cases and hydronephrosis was also quite slight. In my experiment, the new bone grew in proportion as the postoperative days lapsed, and microscopic observation showed that many ossification existed and was connected to each other. The secondary and the tertiary formation of granulation owing to recurrent cystitis might have remarkably accelerated growth of the bone-tissue. It has to be, however, noticed that bone formation did not give any disturbance to the function of the bladder, but on the contrary, it was of help to prevent cicatricial contraction. I should like to study the significance of this ossification further in future.

5. *Urinary Stone.* De MUTH, BARET, and others did not recognize any formation of stone and said that it might be because epithelization of the repaired portion of the bladder would prevent stone formation. In my experiment a stone of small finger tip size was found in one case. It may have been formed, fixing thread of the ureters as its nuculeus.

6. *Regenerating Ability of the Urinary Bladder.* There are many experimental and clinical reports concerning wonderful regenerating ability of the urinary bladder. SCHWARTZ, using dogs, proved successfully possibility of regeneration of a bladder by implanting ureters into the upper portion of the urethra, following total cystectomy. PARLMAN confirmed this fact and considered that the regeneration of the bladder would develop from the urethra. SCHILLER, using rabbits, reported about regeneration of the bladder after subtotal cystectomy which consisted of three layers, transitional epithelium, connective tissue and smooth muscle. FOLSOM and his associates, using dogs, tried also the same kind of experiment and repored that the bladder with all three layers had been newly generated. There are many other clinical reports. In one case of my experiment where a very small portion of the

bladder neck was preserved, the regenerated bladder of 50 cc in capacity was established in 13 postoperative months, while the mold used in the operation was 25 cc in volume; and the lower half of the regenerated bladder was re-grown out of that remained small portion of the bladder neck and presented microscopically a picture just like the normal urinary bladder, and the new bladder as a whole was functioning satisfactorily.

It was noticed that the regenerated bladder would gradually undergo contraction due to cicatrization after the second operation. If the urethral sphincter is utilized, intravesical pressure may prevent contraction, that is, urine stagnated in the bladder may play a role of the mold. The upper portion of the urethra is enlarged into a portion of the regenerated bladder by the intravesical pressure, as is mentioned above. This participation of the urethra to the regeneration of the bladder may rather offset the possible scaring contraction of the regenerated bladder.

Some Suggestions for Future: (1) To preserve the bladder neck or the urethral sphincter. (2) To use a polyvinyl formal mold perfectly disinfected. (3) To make periodical determination of blood electrolytes. (4) To maintain passage of ureteral catheters by clearing at an adequate interval. (5) To remove the mold after 5 to 8 postoperative weeks and ureteral catheters for about 2 weeks. (6) To let the patient urinate regularly at an adequate interval in proportion to capacity of the regenerated bladder, after the removal of the ureteral catheters: urinary catheterization should be continued by night. (7) To place the patient under control of chemotherapeutics and antibiotics, especially it is necessary before and after removal of the mold.

I believe that it is possible, clinically too, to establish a regenerated bladder almost satisfactorily, if the conditions mentioned above could be satisfied.

CONCLUSION

In my experiment, two methods were tried to reconstruct a urinary bladder following total cystectomy. One was a method in which a substitute bladder was formed from a portion of the terminal ileum, and the other in which a new bladder was regenerated from perivesical fatty tissue by means of inserting a mold;the former was applied to 15 dogs and the latter to 14 dogs.

In almost all cases of the experiment, histological investigation was performed.

I. Ileum Bladder. Mucosa of the ileum bladder did not show any morphologic change for 10 postoperative months and presented a histologic picture of normal ileal mucosa. The junctions of the ureter and the urethra to the ileum bladder were rapidly lined with transitional epithelium after the operation, but it was rather intestinal mucosa which grew over the scar in the long survived cases. The ileum bladder wall gradually thickened postoperatively, increasing its capacity. After 10 months, smooth muscle fibers of the ileum bladder hypertrophied and increased both the length and the width by two times, to increase its capacity about tenfold. By full-thickness side-to-end ileoureterostomy, proliferation of the connective tissue between the ureteral stumps and the ileum bladder was successfully checked to the

minimum and patency of ureteral orifices was well maintained. But ureterorenal reflux could not be prevented, and ascending renal infection was found so mild that it was possible to control with antibiotics, in almost all long survived cases. Ileourethrostomy showed complete union almost indistinguishably, both grossly and microscopically, after 10 months. It was very much interesting fact that urinary continence could be maintained by side-to-end ileourethrostomy even in the dogs without urethral sphincter, but it was impossible to explain the reason for it satisfactorily.

II. Regeneration of the Bladder. A pouch of chronic inflammatory granulation was formed within the perivesical fatty tissue surrouding a mold in 3 weeks after insertion of the mold. In 8 weeks the pouch had completed the form as a regenerated bladder; that is, the wall which consisted of mature fibrous connective tissue contained numerous bundles of smooth muscle and its intraluminal surface was lined perfectly with transitional epithelium. It was proved that the new bladder, since then, was playing satisfactory function as a urinary reservoir. In three long survived cases of more than 2 months, bone formation was demonstrated in a small area on the regenerated bladder wall. But this fact, however, did not seem to disturb functional activity of the regenerated bladder as a urinary reservoir. In my experimental survey, the smooth muscle appeared in the new bladder wall was unable to give contracting power to the bladder yet. It is necessary to explore the possible contribution of the smooth muscle to functioning ability of the regenerated bladder. In the dogs which survived for 2 to 13 months, there was histologically no evidence of acute ascending renal infection.

In closing my article, I would like to express my hearty appreciation to Prof. Yaemon Shiraha, M. D. and Assistant Prof. Naohiko Harada, M. D., who have given me kind guidance all through this study and revised this paper in detail. Furthermore, I have to express my gratefullness to the co-workers, Dr. N. Sano, Dr. T. Tsuda, Dr. Ch. Iwade, Dr. K. Fukuyama and Dr. K. Oda, who have shared hardship of this study, and to all the members of Shiraha's department of Surgery who have constantly offered co-operation and conveniences to me. An abstract of this article has been reported at annual meetings of the Japanese Surgical Association on April 29, 1956, and of the Japanese Urological Association on July 7, 1956.

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和文抄録

人工膀胱に関する研究とくにその組織学的研究

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近年骨盤外科，とくに膀胱全剔除術および骨盤内臓器全剔除術の行われる機会が増加しつゝある．しかしかような骨盤外科の分野では，外科医は尿路の変更という未解決の問題に必然的に遭遇する．そこで，この問題の解決に向つて一歩をすゝめるために，(1)本来の尿路の連続性を維持し，(2)尿路の上行感染ができるだけすくなく，(3)尿失禁を伴わず，(4)尿成分再吸収の危険もすくなくて，(5)術後の機械的操作の容易な代用膀胱を作る目的で，つぎの如き2種類の実験を行つた．

Ⅰ) 15匹の雌性成犬を用い，膀胱剔除後，廻腸末端よりの遊離腸管分節を使用し，尿管廻腸尿道吻合術を行つて，代用廻腸膀胱を形成してみた．

Ⅱ) さらに，14匹の雌性成犬において，膀胱剔除後 resin mold および polyvinyl formal mold を使用して，膀胱周囲脂肪組織によつて膀胱を再生させた．

実験動物の術後経過を観察し，日数の経過にしたがつて，尿路の組織学的検査を行い，つぎにのべるような結果をえた．

Ⅰ) 代用廻腸膀胱

1) 廻腸膀胱の粘膜は術後10ヵ月間，形態学的変化を示さず，粘膜上皮は多数の胚細胞をもち，さかんな分泌像を示した．

2) 尿管および尿道と，廻腸膀胱との吻合は早期に一期癒合を営み，術後10ヵ月目には，肉眼的にも顕微鏡的にも識別しがたいほど完全な癒合が成立していた．このさい，吻合部の内腔面は術後速かに移行上皮細胞によつて覆われるが，長期存例においては，むしろ腸粘膜が吻合部を越えて尿管および尿道に向い増生する傾向を示した．

3) 全層・端・側・尿管廻腸吻合術を行えば，吻合部における結合織増殖，およびそれに継発する瘢痕性収縮を最小限に抑制し，尿管開口部の通過性を確保しえて，術後の機械的操作を容易にすることができた．

しかし，ureterorenal reflux はこれを避けることができず，長期生存例のなかには，軽度ながら上行性腎感染が存在した．もち論，この程度の感染は抗生物質を適宜に投与することによつて容易に抑制しうるものと考えられる．

4)廻腸膀胱壁の滑平筋線維は術後次第に肥大し，10ヵ月後にはその長さ，巾ともに正常廻腸壁のそれの約2倍にまで肥大しており，同時に廻腸膀胱の容量は手術時の約10倍に拡張していた．なお，廻腸膀胱は本来の腸管運動能を保持しており，代用膀胱としての機能をはたすことが証明された．

5) 膀胱剔除にさいして，尿道括約筋を同時に切除された犬に対しても，側・端・廻腸尿道吻合術を適応すれば，尿失禁を防止することができるが，これは非常に興味ある事実である．

Ⅱ) 再生膀胱

1) Mold 挿入後3週間で，これを包んでいた膀胱周囲脂肪組織の内側に，(i)内腔面を覆う炎症性偽膜，(ii)線維母細胞の厚い層，(iii)繊細な線維性結合織の薄層よりなる慢性肉芽性嚢状体が形成された．

2) 術後3～5週で mold は除去され，mold 挿入後8週でこの肉芽性嚢状体は再生膀胱としての形態を完成していた．すなわち，(i)内腔面を覆う数層の移行上皮細胞，(ii)未熟な線維組織の薄層，(iii)多数の滑平筋線維束を含む成熟結合織の厚い層，(iv)最外側の脂肪組織層よりなる再生膀胱がえられた．さらに，この再生膀胱は，それ以後尿貯溜器としての機能をはたすことが証明された．

3) 長期生存例において，再生膀胱壁の小範囲に結合織より転化したかと思われる骨組織の新生がみとめられた．しかし，この新生骨は代用膀胱としての再生膀胱の機能をなんら障害しないようである．

4) 再生膀胱壁には滑平筋線維束が出現するが，これは術後13ヵ月目でもなお，再生膀胱に対して収縮機能を与えうる程組織化されてはいなかつた．しかし，今後この滑平筋線維がいかなる態度をとるかをさらに追求する必要があると考える．

5) 術後2～13ヵ月間生存した犬においては，組織学的にも急性上行性腎感染は証明されなかつた．

以上の如く，わたくしは機能的にも組織学的にも，ほゞ満足しうる2種類の人工膀胱を実験的に形成することに成功した．この人工膀胱は将来臨床的にも応用しうるものと考えられるので，とくに臨床応用にさいしても参考となるべき若干の指針を附記した．