THE FEASIBILITY OF PREPARING AN IDEAL SUBSTITUTE FOR THE URINARY BLADDER

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by

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" Skinning is somewhat like crystallization, it requires a surface to shoot from . . . "
" Skinning is a process in which nature is always a great economist, without a single exception."
—JOHN HUNTER (1812) *Blood, Inflammation and Gunshot Wounds* **1**, 362.

HUNTER THE SCIENTIST was fascinated by the healing and regeneration of many different tissues. He might well have been intrigued by the concept that one could replace the mucosa of the intestine by a new lining derived by " shooting " from the implanted ureter. Hunter the Surgeon would certainly have asked: " Why should anyone want to reline the intestine? " The answer comes from the need to replace the urinary bladder after total cystectomy.

To-day, radical resection for carcinoma of the bladder can yield a five-year survival rate of more than 50 per cent if the operation is performed when the tumour is still confined within the bounds of the muscle of the bladder (Higgins, 1961; Whitmore and Marshall, 1962; Bowles and Cordonnier, 1963). Unfortunately, the necessary diversion of urine is so dangerous, accounting for such a considerable share of the postoperative mortality, that the most active supporters of radical surgery in the pelvis are, paradoxically, the most reluctant to advise it in those early cases where alone a cure is possible. So local resection, with or without some form of radiotherapy, remains the usual treatment for these tumours, with results which are typical of half-hearted surgery for cancer in any situation. A proper trial of radical resection would only be justified by a better method of diversion of urine.

In searching for such a method, the animal laboratory proves to be particularly treacherous in this field. For example, it has been known for many years that one may remove the whole of the bladder in lower mammals, anastomosing the ureters to the urethra, and a serviceable new reservoir will form in time (Schwarz, 1891; Aglietti *et al.*, 1961; Kazon, 1963). It seemed not unreasonable to hope that the same thing would happen in man, especially when partial cystectomy, sparing only the trigone, was often followed by restoration of bladder capacity (Fenwick, 1911). It was not even necessary to close up the stump of bladder which was left: it could simply be drained, and in time the bladder would regenerate; an accidental finding (Sisk and Neu, 1939) which has recently been used deliberately (Liang, 1962; Tucci and Haralambidis, 1963).

Unfortunately in man (unlike the dog) it is always necessary to leave the trigone, contrary to the principles of *en bloc* resection for cancer. Not surprisingly, amongst the small number of cases which have been reported, there are several with early recurrences of the vesical neoplasm (Liang, 1962). For the same reason attempts to preserve trigone or prostatic urethra and replace the resected bladder by bowel are also followed by a rather high proportion of early recurrences (Giertz and Franksson, 1957; Deliveliotis, 1963; Couvelaire and Cukier, 1963).

A more promising approach was that of Bohne, Osborn and Hettle (1955). They performed a total cystectomy in the dog, and inserted a plastic mould between ureters and urethra. A fibrous tissue shell formed around the mould, which in time became lined by transitional epithelium. At first it was thought that the fibrous tissue shell was true regenerated bladder, complete with smooth muscle fibres, a finding which was, however, not confirmed when the experiment was repeated (Tsuda, 1958; Swinney *et al.*, 1961; Johnson *et al.*, 1962; Tsuji *et al.*, 1963). Unfortunately, when this operation was performed in man, as soon as the mould was removed the pouch contracted, and, whilst a lumen remained, reflux took place up the ureters. Studies are still continuing along these lines (Tsulukidze *et al.*, 1964), but, even if the problem of contraction is overcome, it is difficult to envisage a satisfactory urinary reservoir with a wall of inert fibrous tissue which has neither elasticity nor contractility of its own. The case reports where this technique has been used in man are discouraging (Bohne and Urwiller, 1957; Tsuda, 1958; Portilla *et al.*, 1958; Bohne *et al.*, 1961; Uhlir, 1963; Tsuji *et al.*, 1963).

Similar criticisms apply to attempts to replace the bladder with a plastic material. There have been many attempts. In most instances the plastic has ended up as a foreign body lying free within the lumen of a shell of fibrous tissue (Swinney *et al.*, 1961). Continuity of tissue between the edge of the plastic and the bladder itself was only achieved when ivalon sponge was used (McDonald and Deniz, 1962). Even here the end-result was a stiff, thick, inflamed diverticulum lined by granulation tissue and calcareous debris, without any transitional epithelial lining, and without contractility. Apart from the difficulties of forming a bond between living and dead tissue, the presence of urine adds the problems of calculus formation. Even a virtually unwettable plastic such as teflon will act as the nucleus for a calculus in presence of infected urine (Dean and Miller, 1962). Advances take place so rapidly in the field of plastics technology that it would be foolish not to keep a hopeful attitude to this approach, but, even if all the technical problems are overcome, such materials will only provide an inert bag, not a self-emptying and lively reservoir.

So much for the results of animal experiments. What are the practical alternatives open to the surgeon to-day? First, he may make an external urinary fistula. This is one possible answer. Nephrostomy is not

acceptable; it carries a mortality of 50 per cent, inevitable infection, and at least 43 per cent calculus formation (de Vries, 1955). Cutaneous ureterostomy in cases with cancer of bladder or pelvis carries a mortality of some 30 per cent (Humphreys, 1956; Couvelaire and Cukier, 1963), and a stoma problem for which numerous answers in the literature testify to the want of any real answer in practice. To-day its place is reserved for the treatment of some children with some neurogenic bladders, particularly when it is not intended as a permanent form of diversion (Eckstein, 1963; Rickham, 1964).

A urinary fistula is much easier to manage if a length of intestine is interposed between ureters and skin. The collecting apparatus is easier to fit, and the stoma is less liable to undergo stricture or retraction. It is now 14 years since Bricker (1950) revived the operation: how does it measure up to-day as a method of urinary diversion after cystectomy? Excellent results are obtained with benign conditions, especially in children; how good is it after cystectomy for cancer?

TABLE I

MORTALITY AND MORBIDITY WHEN ILEAL CONDUIT IS USED FOR DIVERSION AFTER CANCER RESECTIONS

Series	*Number*	*Mortality per cent*	*Morbidity per cent*
McInnes and Engler, 1956	19	10.5	41.2
Baker and Graf, 1956	13	15.4	45.5
Smith and Galante, 1958	30	10.0	52.0
Parkhurst and Leadbetter, 1960	91	14.3	41.0
Levin, Sneider and Andrews, 1961	11	45.5	50.0
Murphy and Mikuta, 1961	26	15.4	—
Hodges, Lehman, Moore and Loomis, 1961	83	8.4	29.0
Butcher, Sugg, McAfee and Bricker, 1962	307	12.4	35.4
Bowles and Cordonnier, 1963	146	5.4	31.5

On reviewing the literature, one of the features which stands out is the high mortality for the operation (Table I). With increasing experience this can be reduced to a figure as low as 5.4 per cent (Bowles and Cordonnier, 1963). The postoperative morbidity, however, remains very high. Most surgeons reporting any large series comment on the incidence of burst abdomen and protracted ileus. For those patients who survive these hazards the stoma brings problems of its own, and frequently requires revision.

The one feature of the ileal conduit which commended it as a method of urinary diversion was its supposed freedom from the metabolic complications of absorption of urine. Even this may be called in question. Hopewell (1959) showed that changes in serum electrolytes are only seen at a stage when the kidneys are unable to cope with the increased burden caused by the absorption of water, urea and electrolytes. When electrolyte imbalance is detected it marks the end, not the beginning, of a pathological process. Of those cases in the literature where details are given

of electrolyte measurements after operation, 83 out of 729 had acidosis, an incidence of 11.4 per cent (Table II). By no means all of these cases were ill; in some the alterations were slight and easily held in check with alkalis. What this figure signifies is that absorption of urine can and does take place in these patients—that the ileal loop is by no means an inert conduit. The longer the loop, the more dangerous; but any length imposes some extra work upon the kidneys. The better the kidney function and the shorter the loop, the smaller the risk of metabolic imbalance; but even if one starts off with a short loop it may double or treble its length in time (King and Scott, 1962). How often, in carcinoma of the bladder, are we going to start off with patients with perfect kidney function? In

TABLE II

ACIDOSIS AFTER ILEAL CONDUITS

Series	*Number of cases with data for electrolytes (survivors)*	*Acidosis noted*
McInnes and Engler, 1956	17	0
Jude, Harris and Smith, 1959	22	9
Cordonnier and Nicolai, 1960	207	6
Burnham and Farrer, 1960	75	19
MacKenzie and Ankenman, 1960	35	6
Creevy, 1960	82	15
Parkhurst and Leadbetter, 1960	78	1
Dennis, Bradshaw and Lynch, 1961	6	3
Levin, Sneider and Andrews, 1961	6	3
Kerr, Robson, Russell and Bourque, 1962	178	10
Couvelaire and Cukier, 1963	5	2
Straffon, Turnbull and Mercer, 1963	18	9
Total survivors with electrolyte data	729	83
	Total with acidosis =	11.4%

practice many surgeons have found a strikingly high incidence of acidosis when using the ileal conduit after cystectomy for cancer of the bladder (Jude *et al.*, 1959 [44 per cent]; MacKenzie and Ankenman, 1960 [17 per cent]; Dennis *et al.*, 1961 [50 per cent]; Couvelaire and Cukier, 1963 [40 per cent]).

The colon may be less absorbent than the ileum (Murphy *et al.*, 1955; Fabre *et al.*, 1958), so that there may be a marginal advantage in using sigmoid as a conduit. So far there are insufficient data to tell whether this applies in man, although obviously the sigmoid would seem to be the most easily available bowel to use as conduit after pelvic evisceration (Goodwin, 1958; Turner-Warwick, 1960). A more practical reason for using a loop of sigmoid as conduit is that many surgeons have had fewer postoperative complications with this procedure than with the formation of an ileal conduit.

Clearly an entirely non-absorbent conduit would be preferable. In the experimental animal these have been constructed from a number of tissues including stomach (Sinaiko, 1956, 1960), the lining of the bladder (Harada *et al.*, 1960) and even skin (Keshin and Fitzpatrick, 1962). All of these have drawbacks: so far none of them has won a place in human surgery. At best they would be external fistulae, and the patient would still need to wear a bag.

To keep the patient dry one may enlarge a conduit into a reservoir, if the opening is kept small. The right colon may be used in this way, having either appendix or terminal ileum as opening (Makkas, 1910; Gilchrist *et al.*, 1950). So far no figures have been published for the actual incidence of acidosis after this procedure, though it must surely occur. Occasional long-lived successes are reported (Bjersing, 1963), and so are failures (Schmitz, 1955; Jones, 1962).

The standard way to form a reservoir remains ureterosigmoidostomy. In the century since this was conceived by Simon (1852) an enormous literature has accumulated, chronicling many arid controversies which we may safely leave undisturbed this afternoon. There is no need to be reminded that reflux and pyelitis are common, or that a valvular anastomosis is not a complete protection against these complications. The conventional wisdom of surgery now accepts that urine is absorbed by colonic mucosa, and that this leads to diuresis, hypertrophy and later destruction of renal tubules. We are aware that potassium is lost both in colonic mucus and possibly also through the kidney, under the influence of an increased secretion of aldosterone (Hayward *et al.*, 1961), leading to a total body deficit of potassium, sometimes of severe proportions. For all these reasons some surgeons have given up the operation altogether, and others reserve it for palliation. All would give it up if they were satisfied that they had a better alternative.

Many of these disadvantages of ureterosigmoidostomy can be avoided if the sigmoid is divided, the proximal end brought out as an abdominal colostomy, and the isolated rectosigmoid " bladder " used to form a urinary reservoir. This is continent because of the anal sphincter. It is safe, not only because the peristaltic pressure is lower in the rectum than the rest of the colon so that reflux is less apt to occur (Smith and Hinman, 1955), but also, when it does, the urine is not mixed with faeces. The dry colostomy is more acceptable to many patients than a wet one. The operation is hardly more time-consuming than ureterosigmoidostomy itself, and, as Pyrah (1963) has pointed out, it may for safety be done in stages. Yet for all these advantages the urine is still confined within an absorbent reservoir, and acidosis can still be detected in a substantial proportion of the patients (Table III). Once again, few of these patients are ill: the electrolyte imbalance is a laboratory finding, not a clinical one.

The fact that it may occur, however, indicates that significant absorption does take place—absorption which it would obviously be desirable to prevent.

From the isolated rectosigmoid bladder it is a short step to the attempt to bring the colostomy through the anal sphincter instead of out on the abdominal wall. Surgeons have been attempting this feat since 1898, and more than a hundred cases have been reported since Gersuny's original description. We do not know how many more went unreported. Jonothan Hutchinson (1890) remarked, " as regards operation cases probably not a fifth of those which are unsuccessful find their way into type ". In this country attempts to make a perineal colostomy have an evil reputation. An incontinent anus can hardly be sited in a more awkward place. But it may be that the time has come to re-examine this

TABLE III

ISOLATED RECTOSIGMOID BLADDER

Series	*Survivors with electrolyte data*	*Acidosis*
Kinman, Sauer, Houston and Melick, 1953	8	1
Melick and Naryka, 1955	6	1
Paull and Hodges, 1955	5	4
Wilkins and Wills, 1959	6	0
Wallace, 1961	4	3
Magendie, Lassalle, Despruniée, Galy and Planès, 1961	1	1
Kerr, Robson, Russell and Bourque, 1962	75	9
Pyrah, 1963	26	4
Total survivors with electrolyte data ..	131	23
	Acidosis =	17.6%

idea in the light of fresh evidence. On the clinical side, although Goligher and Hughes (1951) came to the conclusion that it was necessary to preserve at least 10 cm. of rectal mucosa if a patient were to be continent after anterior resection, recently several series of pull-through operations for carcinoma of the rectum have been published in which hardly any rectal mucosa is preserved without loss of continence (Black, 1959; Hughes *et al.*, 1962; Ravitch, 1961; Stephens, 1953). From the laboratory the work of several groups is causing us to revise our notions of the physiology of the anal sphincter, emphasizing the importance of its external component (Parks and Porter, 1962; Phillips and Edwards, 1962; Bennett and Duthie, 1962).

Following the lead of Marion himself (Heitz-Boyer and Hovelacque, 1912), French surgeons have never given up the attempt to bring faecal and urinary streams through a common sphincter. To-day Duhamel reports success with his version of this operation without loss of control either of

faeces or of urine (Duhamel, 1957, 1962). It seems probable that the next few years will see this surgical technique perfected, standardized and accepted. The single obstacle then remaining in the way of an ideal substitute for the urinary bladder will be the absorption of urine.

As mucosal absorption is an active metabolic process it can be abolished by radiation. Irvine *et al.* (1960) used colloidal Yttrium-90 to reduce mucosal absorption without abolishing the motility of the colon in the dog. But the method is fraught with technical difficulties, including that of calculating the dosage and the radiation hazard to attendant personnel. As yet it seems far from clinical application.

An alternative possibility is to do away with the absorbent mucosa of an intestinal reservoir, and reline it with urothelium*—a layer of cells which has some very remarkable properties, two of which deserve particular mention.

First, urothelium is almost waterproof. Isotope studies have shown that the movement of water and ions across urothelium is a slow process of diffusion rather than active transport as in the intestine (Levinsky and Berliner, 1959; Rapoport *et al.*, 1960; Kerr *et al.*, 1963). For the purpose of lining a reservoir to contain urine it is perfect—a conclusion which would not have surprised John Hunter.

Where can we find a supply of urothelium when we have removed the bladder and urethra for cancer? In the cut ends of the ureters? This is a small " surface to shoot from " indeed, and brings us to the second remarkable property of urothelium. It is uniquely suited to the task of covering a large surface quickly by migration, spreading, or, in Hunter's term, " shooting ". McMinn and Johnson (1955) showed that when an ulcer healed in the bladder, there was not only mitosis on each side of the defect, as one would find in skin or intestinal mucosa, but that the migrating cells themselves underwent mitosis; a situation as if an advance party could supply its own reinforcements instead of having to bring them up from the rear. Relining a surface in the urinary tract can thus be exceedingly swift. What is more important, the origin of the urothelium need only be very small, so that it is not entirely absurd to expect the implanted end of the ureter to furnish enough to reline a urinary reservoir of appropriate size.

The next question was what material would make the best scaffold for this new lining? Many different tissues have been placed in the bladder

* The layer of cells lining the urinary tract has unique features. It forms no mucus, and is not mucosa: it is anatomically an endothelium, not an epithelium. *Transitional epithelium* is a translation of " uebergangsepithelium " (Henle, 1866), but has little else to commend it. *Urothelium*, coined by Narath (1951) is North American usage, and has no more absurd an etymology than *Epithelium* (ουρον = urine: θηλη = teat *O.E.D.* 1933). Urologists may use it without scruple.

as patches since Neuhof (1917) first used fascia lata for this purpose. It is found that if a tissue has an epithelium of its own it will keep it, but if it has none, or only a covering of serosa, then urothelium will migrate

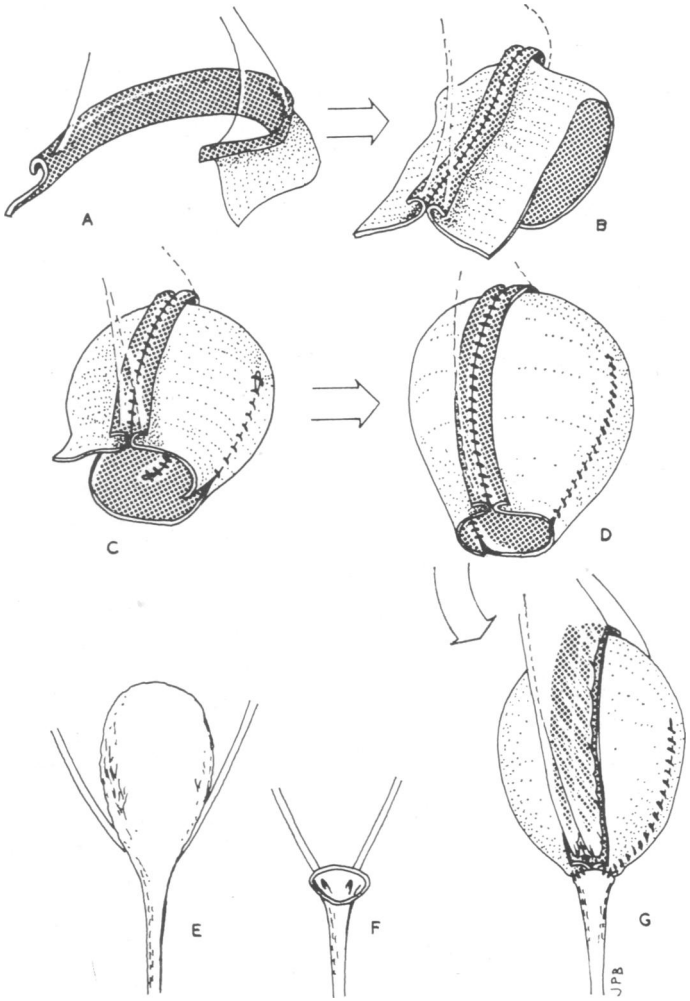

Fig. 1. Construction of full thickness reversed " ileo-entrectropy " pouch with anastomosis to remnant of bladder after subtotal cystectomy. A = isolated loop opened near mesenteric attachment. B = first row of sutures completed, second fold started. C, D, G, completion of pouch and anastomosis to trigone.

over it to reline it (Sanders and Schein, 1956). So, to use intestine for the reservoir, it is necessary either to turn it inside out, offering serosa to the spreading urothelium, or to remove the mucosa completely.

The first of these alternatives, to turn the bowel inside out, would leave the intestinal mucosa facing the peritoneal cavity. It is claimed that this may be done without ill effect. The operation of ileo-entrectropy was devised in the dog and applied to man in the treatment of ascites (Neumann *et al.*, 1956, 1957).

As it was known that the ileum, right way round, had a contractility which served it satisfactorily as a substitute for the detrusor of the bladder

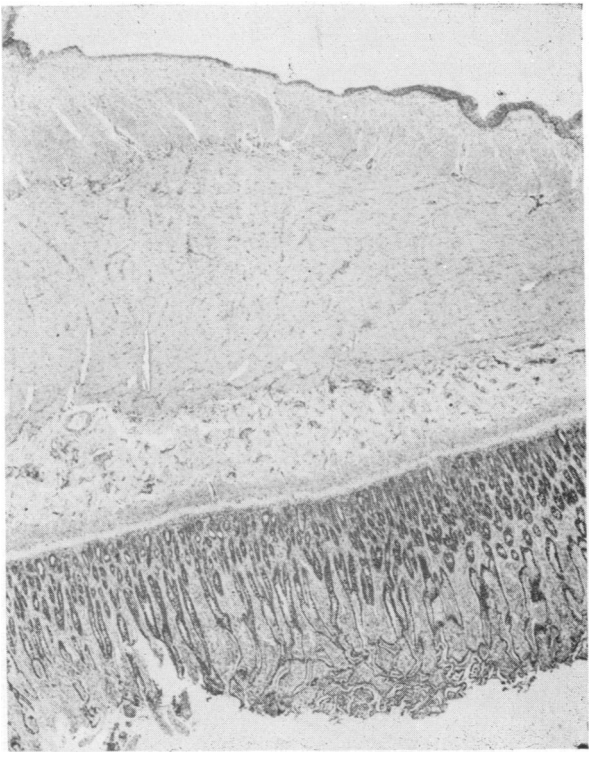

Fig. 2. Reversed ileal pouch after 21 days; death with peritonitis. Section (H. and E. × 12) through wall of pouch showing urothelium spreading over the serosal surface of the ileum: mucosa on the other surface.

(Truc and Grasset, 1961), it seemed possible that similar motility might be found in a hollow reservoir constructed from full thickness intestine turned inside out. If this could be provided with a new lining of urothelium then it might well form a perfect substitute for the bladder. It was decided to put this to the test.

Isolated loops of ileum were formed in 10 dogs (Fig. 1), turned inside out, and formed into hollow pouches. To see whether urothelium would spread over their serosa they were anastomosed to the trigone (8 dogs) and in two a single ureter was implanted, and the mouth of the pouch brought to the skin. The animals were sacrificed at intervals, and the pouches examined histologically.

It was found that urothelium did indeed spread (Fig. 2) over the serosa on the inside of the pouches but, while this was taking place, there was a striking accumulation of mucus on the outside of the pouch, and every animal had mucous peritonitis with pockets of inspissated mucus and widespread peritoneal adhesions.

This was not merely due to the presence of urine in the lumen of the pouch, for it was also found in three control pouches in which no anastomosis had been made to the urinary tract.

From these results (Table IV) it became clear that in my hands, and in the dog, an ileo-entrectropy preparation was not suited to the formation of a urinary reservoir. (These findings led us to re-examine the published accounts of ileo-entrectropy in man. There were accounts of 15 human cases: six died of the operation and at least three of the nine survivors were

TABLE IV

FULL THICKNESS REVERSED "ILEO-ENTRECTROPY" POUCHES

Survival	*Cause of death*	*Urothelial lining*
Controls: not anastomosed to urinary tract		
77 days	peritonitis	nil
166 ,,	sacrificed (peritonitis)	nil
140 ,,	,, ,,	nil
Anastomosed to trigone after subtotal cystectomy		
3 days	urine leak	nil
3 ,,	peritonitis	nil
4 ,,	peritonitis (sac)	nil
14 ,,	,, ,,	present
21 ,,	,, ,,	,,
28 ,,	,, ,,	,,
38 ,,	,, ,,	none present: secondary infection ++
56 ,,	,, ,,	present
Anastomosed to single ureter: cutaneous stoma		
23 days	peritonitis (sac)	present: secondary infection
62 ,,	,, ,,	present

noted to have pockets of mucus and multiple adhesions [Mulholland, 1957; Leger *et al.*, 1959; Girling, 1959; Macby, 1960]).

The next logical step was to remove the mucosa. Shoemaker and his colleagues, in a series of papers from 1954 onwards (Grotzinger *et al.*, 1954; Shoemaker *et al.*, 1955–59), reported satisfactory migration of urothelium over the serosa of a "reversed seromuscular ileal graft" in which the mucosa was separated from the submucosa and the graft turned inside out. The reason why they reversed the graft was that mucosa tended to reappear on the submucosa, and so prevented the successful colonization of the surface by urothelium. No trouble, however, was reported from the formation of mucus in the peritoneal cavity in an extensive experience with the procedure. It seemed reasonable to use a similar preparation of ileum.

In three dogs the mucosa was scrupulously removed from the submucosa in isolated ileal loops by prolonged scraping. The mucosa-free loops were then folded and sewn into the shape of a hollow sphere (Fig. 3) into which one ureter was anastomosed over a

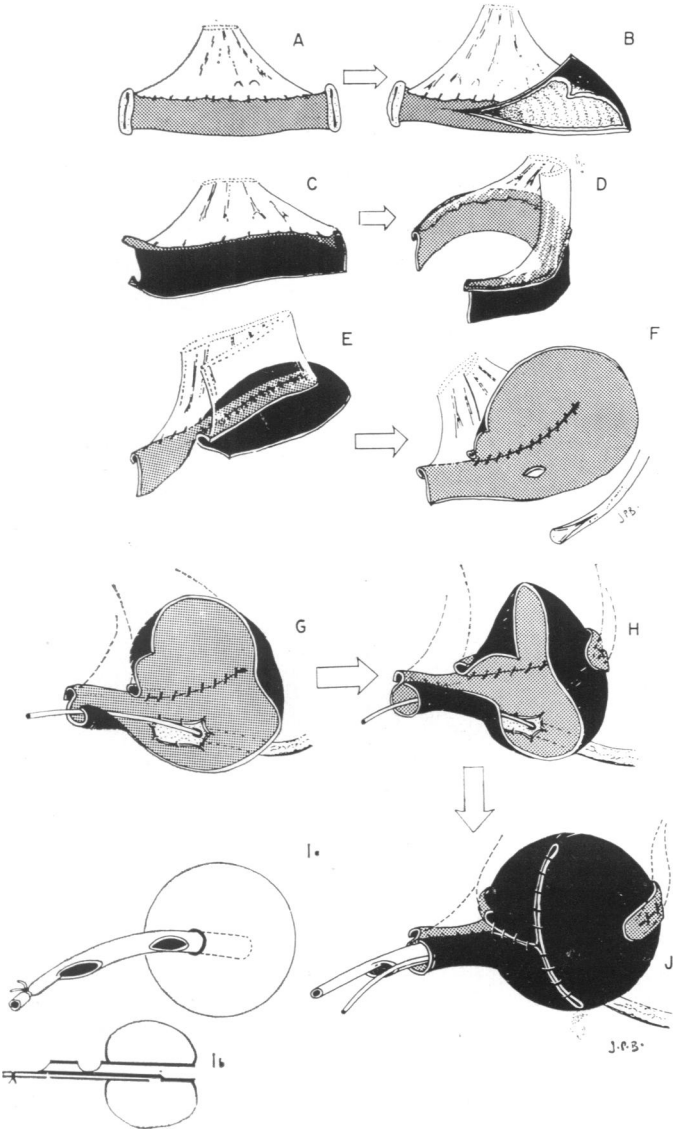

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Fig. 3. Construction of reversed seromuscular ileal pouch from isolated ileal segment. A = isolated ileal segment. B = segment opened near mesentery. C = after removal of mucosa the edge is allowed to curl over. D, E = graft sutured edge-to-edge leaving mesentery on outer side. F = lower end of left ureter prepared for insertion into pouch. G = spatulated ureter sutured to serosa on inner surface of pouch. H, J = completed pouch. Ia, Ib, latex mould used to maintain shape of pouch.

polythene splint. The spherical shape was maintained with an inflatable latex mould which was led out through the skin and changed weekly. Animals were sacrificed at intervals of one, two, and six weeks after operation. Again it was found that urothelium did migrate from the ureter over the serosa on the lumen side of the pouches, but that once again, on the outside of each pouch, the ileal mucosa had re-formed and the animals had mucous peritonitis (Table V).

It was a possibility that with more experience one might achieve complete removal of all remnants of the mucosa, but as even Shoemaker, with his considerable experience with this type of preparation, still found it necessary to turn the graft inside out, presumably because of regeneration of the mucosa, it did not seem worth while to pursue the technique further (Blandy, 1961).

TABLE V

MUCOSA ONLY REMOVED. REVERSED POUCH

Survival	*Cause of death*	*Urothelial lining*
7 days	distemper	nil
15 ,,	sacrifice (peritonitis)	10 per cent—site of ureteric anastomosis only
43 ,,	sacrificed (peritonitis)	complete lining, some secondary infection

Between submucosa and muscle, however, is a plane of cleavage which is easily found. Instead of piecemeal scraping, one can peel a tough sheet of submucosa and mucosa away from the muscle, leaving a graft which lacks much of the strength of the original intestine, but can still be handled and sewn with reasonable care. There were few previous attempts to use this type of graft, and these had met with conflicting results (Shoemaker, 1955; Greenfield, 1959). It seemed worth attempting to effect a more complete removal and so prevent accumulation of mucus in the peritoneal cavity.

TABLE VI

MUCOSA AND SUBMUCOSA REMOVED: REVERSED POUCH

Survival	*Cause of death*	*Urothelial lining*
1 day	ruptured pouch	nil
3 days	infarcted pouch	nil
5 ,,	,, ,,	nil
28 ,,	sacrificed	25 per cent
62 ,,	,,	complete
82 ,,	,,	,,

In six dogs a series of similar pouches were made to the preceding group, the only difference being the removal of submucosa. The grafts were turned inside out and one ureter was implanted as before. Three of the six dogs survived. All of these showed spread of urothelium from the ureter over the serosa, and in one dog there was a complete lining of the pouch by six weeks (Table VI). Three of the dogs died soon after operation, probably as a result of ischaemia from the need to fold over the graft at the mesenteric attachment. None of the animals re-formed ileal mucosa; none had mucous peritonitis.

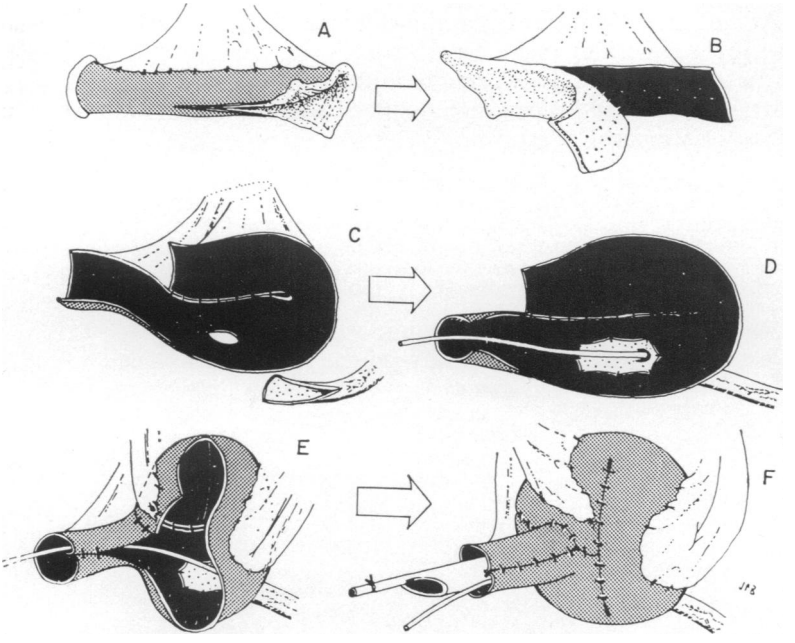

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Fig. 4. Construction of non-reversed seromuscular ileal pouch. A = isolated segment opened on anti-mesenteric border. B = mucosa and submucosa removed. C = graft folded, ureter prepared and D = ureter anastomosed over polythene splint. E, F = pouch completed over latex mould.

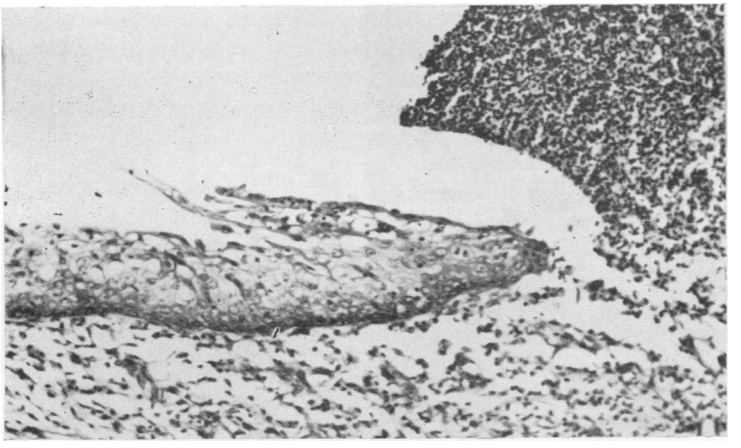

Fig. 5. Fourteen days after formation of pouch urothelium is seen advancing between surface debris and the granulation tissue lining the raw muscle on the inner surface of the pouch. Mitotic figures can be seen in the advancing front of the urothelium.

At this stage it seemed questionable whether there was any need to reverse the graft, if by removing submucosa one prevented the re-formation of the mucosa. If the experience with cystoplasty experiments was to be trusted, the urothelium should spread over the raw intestinal muscle if it had no mucosa of its own.

In 15 dogs similar grafts of ileum were prepared by removing submucosa and mucosa from the muscle, but in these animals the pouches were formed without turning the bowel inside out (Fig. 4). A single ureter was implanted as before. The animals were sacrificed at intervals from the operation, and once again it was found that urothelium spread rapidly from the ureter over the inner surface of the pouch to reline one of up to 60 ml. capacity in six to seven weeks (Fig. 5; Table VII).

TABLE VII

MUCOSA AND SUBMUCOSA REMOVED: POUCH NOT REVERSED

Survival	*Cause of death*	*Urothelial lining*
1 day	shock	nil
2 days	distemper	nil
4 ,,	not determined	nil
14 ,,	sacrificed	20 per cent
23 ,,	,,	50 ,, ,,
43 ,,	,,	90 ,, ,,
55 ,,	,,	full
55 ,,	,,	full
63 ,,	,,	full
64 ,,	peritonitis	secondary loss: incomplete lining
77 ,,	sacrificed	full
78 ,,	,,	,,
80 ,,	,,	full: secondary infection
84 ,,	,,	,,
109 ,,	,,	,,

This preparation was the most satisfactory of the alternatives so far investigated, and it seemed clear that nothing was to be gained by turning the bowel inside out provided the submucosa was removed. So far these findings applied to the small bowel: could a similar preparation be made from the colon?

Few studies had been attempted with the colon. Reversed seromuscular patches of colon had been used for cystoplasty by Shoemaker (1955) and Rovinescu (1961), who both reported spread of urothelium over the serosa of the patches. Passaro and Pace (1962) were more successful: by very prolonged and vigorous scraping they succeeded in removing the mucosa from the rectum so completely that it did not regenerate. Urothelium was furnished by free grafts of the lining of the bladder. From these urothelium spread to reline the rectum, into which the ureters were implanted at a second stage. Despite this my own experience with similar attempts in the ileum led me to suppose that it would be more promising to remove the submucosa in a single sheet rather than attempt protracted scraping in the colon. After all, the aim was a technique which could be readily repeated and standardized.

One of the difficulties in applying canine results to man is that the dog's colon is a very different structure. It is shaped like a question mark; has no distinct sigmoid or ascending colon, neither haustrations nor taeniae. In its blood supply (as we were to find to our cost) there are differences from the arrangement in man. Preparations were made from three different parts of the colon, the transverse, the descending, and the " rectosigmoid ".

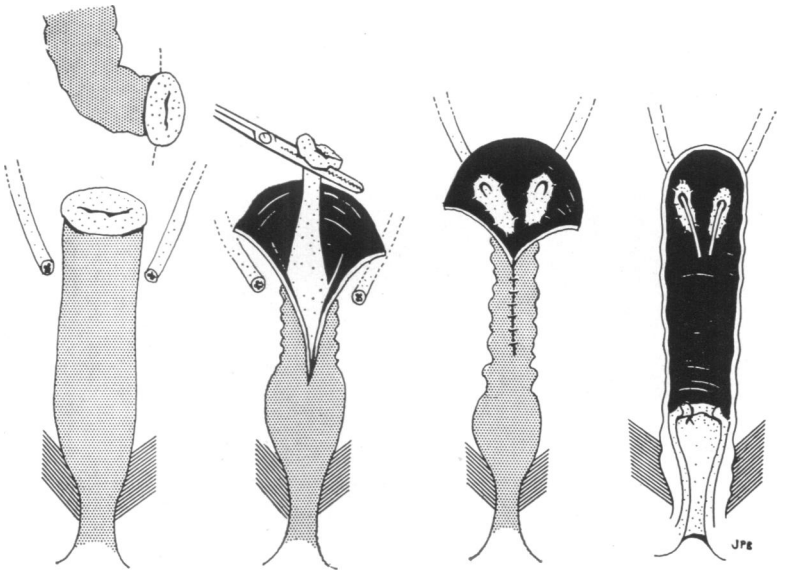

Fig. 6. Construction of non-reversed seromuscular pouch from the " rectosigmoid ". A preliminary end-colostomy is established. The mucosa and submucosa are removed, leaving the muscle into which the ureters are anastomosed. A marker suture indicates edge of remaining rectal mucosa.

Beginning with the transverse colon, pouches were prepared in two dogs. Mucosa and submucosa were stripped off the muscle, which was then sewn into a hollow sphere whose form was maintained by an inflated mould. One ureter was implanted as in the ileum. It was found that urothelium did grow over the denuded muscle, but the mesocolon was so short that the pouch could not be placed anywhere but in the epigastrium, and it was difficult to bring a ureter to it. At least in the dog the transverse colon had limited usefulness.

In seven dogs attempts were made to form pouches from isolated segments of the descending colon. All but one of these, however, underwent infarction. In the survivor the ureteric epithelium was found to have spread a short way over the denuded colonic muscle, but injection studies (Blandy, 1963) showed that to prepare an isolated pouch from the descending colon in the dog must almost inevitably obstruct its venous return, which follows a pattern different from that of man. For all practical purposes this type of pouch is useless in the dog.

Finally, attempts were made to form pouches from the straight last part of the dog's colon, which from its analogy with that part of the bowel in man rather than from its

shape may be called rectosigmoid. In 23 dogs pouches were formed (Fig. 6) by removing the mucosa and submucosal sleeve from the rectosigmoid after bringing the faecal stream out as an end-colostomy. The rectal mucosa was marked with a silk stitch where it was transected. One or both ureters were implanted. The shape of the lumen was maintained by means of an elongated latex mould. Twelve of these dogs survived for more than 10 days after the operation and in these there was spread of the urothelium (Fig. 7) over the raw colonic muscle in all but two dogs: in these two the inner layer of circular colonic muscle had undergone infarction (Table VIII). In successful pouches the urothelium grew over the raw muscle until it met the edge of the

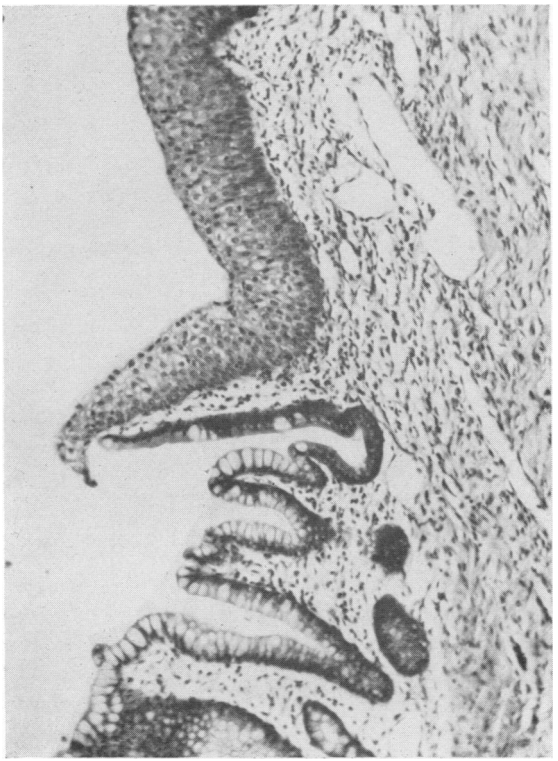

Fig. 7. Section (H. and E. × 120) through site where urothelium has reached the cut edge of the rectal mucosa (below).

rectal mucosa, but the pouches themselves all became greatly contracted because the moulds were removed by the dogs within a few days of operation. Those who survived were apt to lose weight and condition, a difficulty usually seen in a dog with an end-colostomy (*cf.* Buckwalter *et al.*, 1961).

In many of the dogs who did not survive the operation death was due to leakage of urine following infarction of the pouch. This led to a re-examination of the intrinsic supply to the canine colon by a series of injection studies (Blandy, 1963). These confirmed that some of the blood supply to the muscle of the colon came from re-entrant branches from the

vascular plexus in the submucosa (Brockis and Moffat, 1958; Griffiths, 1961), so that when the submucosal plexus was removed by stripping off the submucosa the blood supply to this muscle was likely to be impaired. However, the muscle survived in 10 of these dogs and grew urothelium, and our injection studies were able to demonstrate a second plexus situated between the muscular layers supplied by offshoots from vasa recta and vasa brevia.

It remains an open question whether the special difficulties encountered in preparing this type of pouch from the dog's colon are likely to be seen in man. Certainly the difficulty with an end-colostomy will not arise. Parks (1962) has shown me injection studies in human material where the same intermuscular plexus can be seen in the rectum.

TABLE VIII

RECTOSIGMOID PREPARATIONS: SPREAD OF UROTHELIUM IN SURVIVING ANIMALS. SUBMUCOSA AND MUCOSA REMOVED

Survival	*Urothelial lining*
13 days	nil: inner muscle infarcted
18 ,,	urothelium present
16 ,,	,,
35 ,,	complete lining
38 ,,	,,
41 ,,	nil: inner muscle infarcted
42 ,,	complete lining
42 ,,	,,
48 ,,	,,
48 ,,	,,
50 ,,	,,
52 ,,	,,

However, in the dog there was no doubt that the best reservoir was one made by removing submucosa and mucosa from ileum, leaving its two layers of muscle and the covering layer of serosa. The next question was whether these layers of ileum, with their new lining of urothelium, would still contract and empty when filled. On the face of it this was perhaps unlikely: we were removing both the rich plexus of nerve endings lying in the mucosa as well as the plexus of Meissner with its peripheral ganglion cells situated in the submucosa (Stöhr *et al.*, 1959). Bülbring considered that peristalsis depended on the integrity of the mucosa which contained a pressure-sensitive mechanism (Bülbring, 1961, 1962). Although in Ginzel's preparations the small intestine appeared to respond not to an increase in pressure but to stretching or distension (Ginzel, 1959), even in his preparations the submucosa was not disturbed. If ileal muscle could still respond to stretch by contractions, these might not be sufficiently co-ordinated to be effective if Meissner's plexus had been removed.

What kind of contractility did we need in a urinary reservoir? Certainly it was not necessary to obtain the specialized pattern of motility which goes to make up the normal human cystometrogram: it would be sufficient

if the relined intestine were to retain some degree of elasticity so that filling would cause an increase in the resting tone within the reservoir. It would be better still if distension could, at a certain point (when the reservoir was full), set off waves of contraction, because it was known that patients experienced the sensation of a desire to empty their ileal *néovessies* at the point when these waves of contraction were noted (Truc and Grasset, 1961).

Apart from these studies into the behaviour of ileal *néovessies*, no measurements had been recorded of the motility of the normal thickness of the bowel when formed into a hollow sphere. It was therefore necessary to construct pouches of full thickness ileum and then compare their motility with that of the relined preparation.

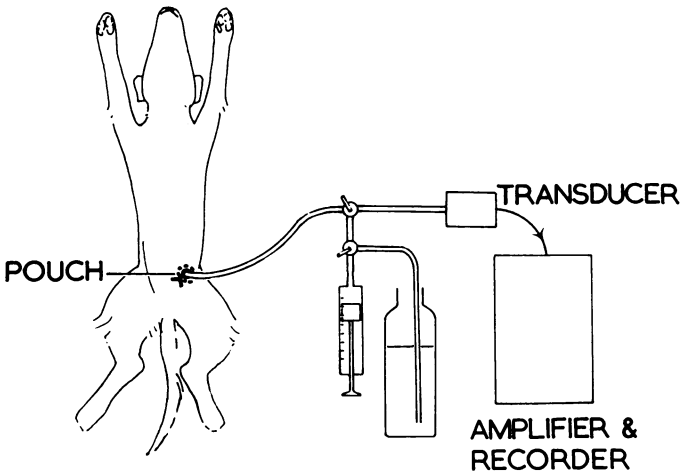

Fig. 8. Method used to study pressure inside pouch in response to filling and to intravenous prostigmine. Catheter secured in stoma of pouch with purse-string is led to transducer. Increments of saline are introduced with the syringe. A pneumograph and oscilloscope were also used (not shown).

Three relined seromuscular ileal reservoirs were made, and two similar pouches having full thickness bowel. The animals were anaesthetized, and the mould was removed from the pouch into which was inserted a catheter, which was secured with a purse-string suture. The catheter was led to a pressure transducer and recording apparatus (Fig. 8). A simple pneumograph was also made to record respiratory excursions on the same trace.

In one series of measurements pouches were filled by increments of 2 ml., and the pressure recorded in between. In another the pouches were filled to half their capacity and prostigmine was given intravenously.

With spherical pouches of full thickness ileum the type of motility in response to increased filling followed a uniform pattern: there was a rise in the basal pressure, then small abortive contractions would appear and die out, and finally, when the pouch was filled, a regular rhythmical contraction would appear. This was virtually identical to the behaviour previously reported with ileal *néovessies* (Truc and Grasset, 1961).

With relined pouches the response to filling was of a similar pattern though the contractions were a little less regular. There was a gradual increase in the basal pressure followed by the appearance of short trains of waves, and finally by the establishment of a long succession of rhythmical contractions (Fig. 9).

Similar contractions were also recorded in these pouches in acute experiments during which they were exteriorized to prevent movements of adjacent bowel from appearing on the record. On these occasions the movement of the wall of the pouch was easily seen.

When prostigmine was given to half-filled pouches a similar pattern of motility was recorded, and in addition to this there was a marked increase in the basal pressure

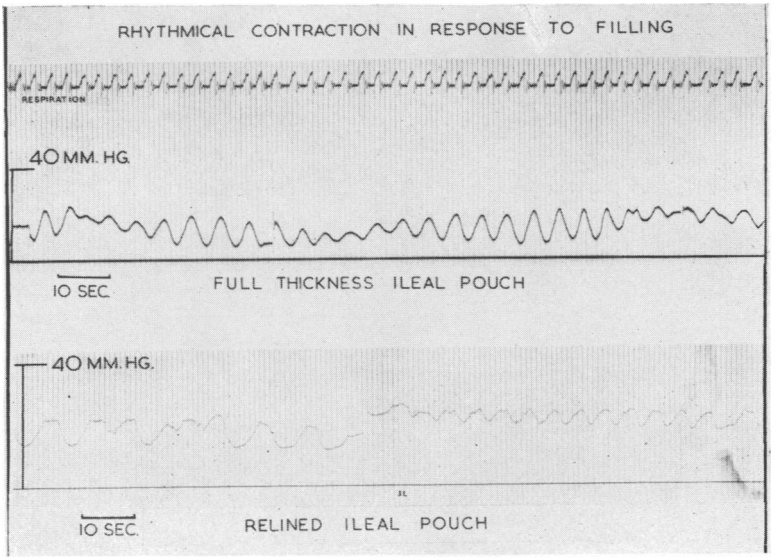

Fig. 9. Comparing the rhythmical contractions obtained in spherical pouches of full thickness ileum (above) with those in the relined seromuscular ileal pouches (below).

within the pouch. Frequently the catheter was expelled at this stage. The contraction of the pouch which accompanied these pressure changes was easily seen in the acute experiments on exteriorized pouches (Fig. 10).

These findings suggested that the relined ileum would perform in a similar way to the ileal *néovessies*, which were known to serve as adequate substitutes for the detrusor. However, these *néovessies* were working in conjunction with the intact sphincter of the bladder. The motility we had so far been recording was obtained in pouches with a cutaneous stoma. As we were envisaging a modification of the Gersuny operation in which the relined rectum would be working in conjunction with the sphincter of the anus, we attempted to see whether such a combination would form a useful urinary reservoir.

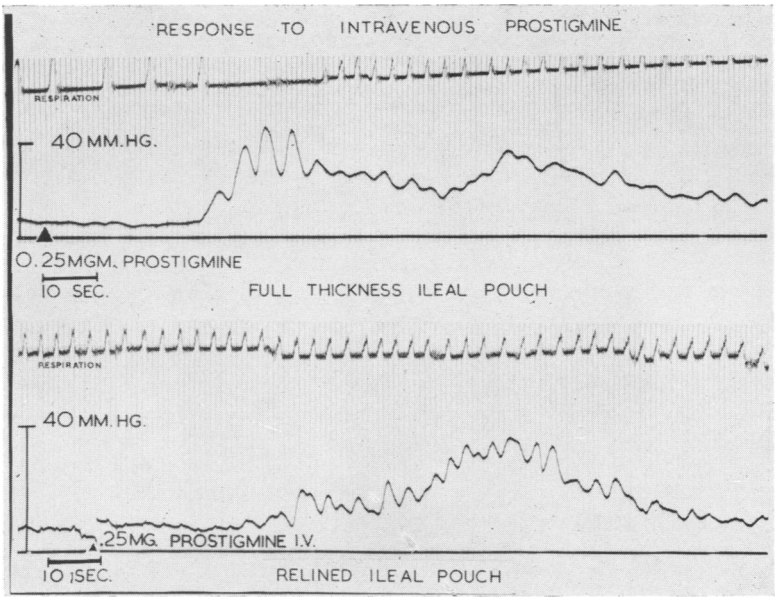

Fig. 10. Comparing the contractions produced by intravenous prostigmine in the full thickness ileal pouch (above) with the relined pouch (below).

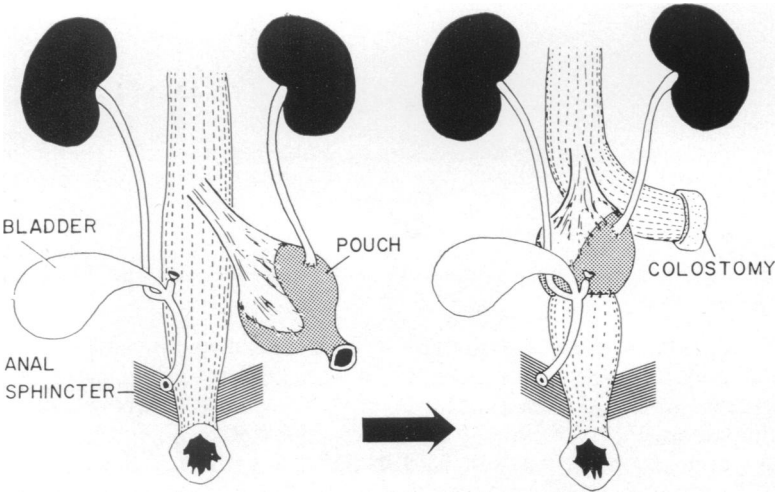

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Fig. 11. Method of constructing a composite reservoir by transferring the pouch from the skin to the distal rectum at a second-stage operation.

Composite bladders were prepared by transferring the pouches from the skin in four dogs to the rectum as far down in the narrow canine pelvis as the anastomosis could be made (Fig. 11). At autopsy one usually found that the residue of the rectum had hypertrophied or elongated, so that the motility which was recorded must to some extent have reflected the response of the rectum rather than the relined ileum (Blandy, 1961). However, the dogs voided through the anus in a normal way and on catheterization afterwards were found to have no residual urine in the composite bladder.

At this stage it seemed that such a preparation would have nearly all the requirements of an ideal substitute for the urinary bladder, but two obvious criticisms had still to be met. First, it was well known that regenerating urothelium had the odd property of inducing new bone formation in underlying tissues—a property which had been intensively

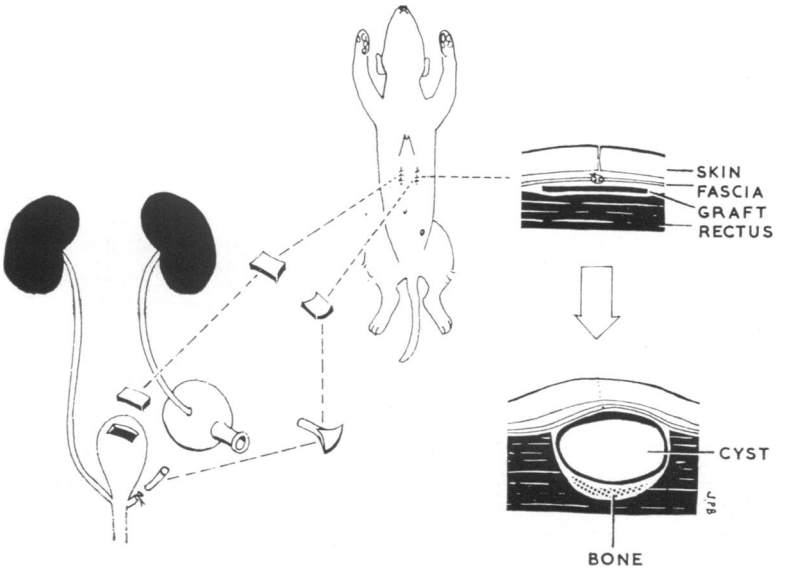

Fig. 12. Preparation used to study heterotopic bone formation in dogs with seromuscular pouches and control autografts of vesical and/or ureteric epithelium under the rectus sheath.

studied by Huggins over 30 years ago (Huggins, 1931). Would this convert the relined reservoir into an inert structure like an egg-shell?

A controlled study was therefore undertaken (Fig. 12) (Blandy and McDonald, 1961) in which, at the time the pouch was formed, small pieces of bladder or ureter were placed under the rectus sheath, the site of the implants being marked with a tattoo of indian ink. The animals were sacrificed at intervals and the implants removed and sectioned. Each little graft formed a small cyst, and as a rule in the wall of the cyst there was a patch of heterotopic ossification. In the whole of this series ossification was never seen in the ileal pouches formed by removing submucosa and mucosa, which were not turned inside out. Ossification

did occur in one colonic pouch of this type, at the site of a silk marker suture, and since these findings were published it has subsequently been seen in two of the ileal pouches which were used in the motility study. It seems likely, therefore, that, whilst ossification may occur, it will be very limited and will not interfere with the contractility of the relined ileum. These findings are in agreement with those of Joseph (1961), who also has found bowel relatively resistant to the induction of heterotopic ossification by urothelium.

The second criticism cannot yet be put to the test of animal experiment: might not regenerating urothelium give rise to neoplasm? Von Brunn's nests are found under healing urothelium in the bladder and are held by some pathologists to be preneoplastic; we saw none in these preparations. Papillomatous outcrops were seen occasionally by Huggins in his transplants to the rectus sheath; none were seen in the present material. In the patients for whom such a bladder substitute might be made the urothelium would arise from a relatively unstable source, from urothelium which had already shown neoplastic change in one situation. As with any field of surgery there comes a stage when the animal laboratory can no longer provide an answer. In man, many of the difficulties which were found in these studies would not be encountered; the difficulty of keeping a mould in place, and the problem of the colostomy are obvious examples. Despite these reservations these animal studies suggest that urothelium will spread rapidly from the ureter to reline intestinal muscle; that intestine is best prepared by removing its mucosa and submucosa; that there is no need to turn it inside out; and that, when relined, the intestinal muscle can still contract in response to distension, and is scarcely affected by heterotopic ossification. These are basic principles. They are unlikely to vary from one species to another.

Perhaps then, not long in the future, we may see a new substitute for the urinary bladder; one lined with non-absorbent urothelium derived from the ureters, able to contract when distended and to signal this contraction as a desire to void, with separate channels for urine and faeces under the voluntary control of the anal sphincter. Dry, safe and acceptable, such a substitute is, I submit, feasible.

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HEROES OF THE EXAMINATION BOOKS

10. Thomas Graves, Lord Graves (1725–1802)

LORD GRAVES HAS had the misfortune to go down in history as the man who might, had he been a Nelson, have relieved Yorktown and perhaps have changed the course of the War of American Independence. This judgement has tended to obscure the merit of his service in the Navy.

Graves joined the Navy at an early age. As a lieutenant he was present at the Battle of Toulon in 1744 and at the Battles of Finisterre and Biscay in 1747. After commanding various ships in the intervening years, he was promoted to flag rank in 1779. The next year he sailed with reinforcements for North America and was appointed Commander-in-Chief on that station in July 1781. In the engagement off Chesapeake Bay on 5th September Graves found himself in a markedly superior tactical position, but with a much inferior force (19 to 24) to the French. A Nelson, by attacking at once and by disregarding the risk of being shot for abandoning the formal order of the Fighting Instructions, might have destroyed the French fleet and relieved Yorktown, but it is unfair to blame Graves for not doing what only Nelson would have attempted.

In 1794 he was appointed to the Channel Fleet as second-in-command to Lord Howe, and played an important part in the victory which became known as the " Glorious First of June ". He was severely wounded in the arm at about 9.50 a.m. This wound brought him before the Court of Examiners on 2nd January 1795, when the Examiners found that the wound was equal to the loss of a limb. He appeared again before the Court on 5th March. On this occasion the entry reads: " Admiral Lord Graves—claimed £210 19s. 6d. for the Expences of his cure and allowed £80 7s. 0d. being the Chirurgical Expences—the Court not deeming themselves proper Judges as to the others."

E. H. C.