Section of Urology

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Reduction in Colonic Mucosal Absorption with Reference to the Chemical Imbalance of Ureterocolostomy

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Introduction

Improvements in technique, together with sulphonamides and antibiotics, have made ureterocolostomy a progressively less formidable procedure from the standpoint of immediate post-operative mortality. Now the late complications of renal damage and electrolyte imbalance are being more closely studied.

Renal damage has long been known to be a serious complication of ureterocolostomy patients and the clinical evidence of this has been reviewed elsewhere (Irvine *et al.*, 1956).

The high incidence of electrolyte imbalance has only recently been recognized. In a series of experimental studies previously recorded (Irvine *et al.*, 1956) evidence was presented that the primary cause of the imbalance was absorption of the urinary constituents across the colon mucosa though renal damage might be expected to increase the biochemical disturbance.

If ionic absorption across the colon mucosa is the important primary factor in chemical imbalance it would seem worth while to investigate means of inhibiting this process. Indeed, in some patients after ureterocolostomy a spontaneous reduction in ion transport into the blood stream and in the differential excess of chloride reabsorption over sodium has been noted to occur (Care *et al.*, 1957). Intraluminal irradiation was well known to reduce the secretory activity of the gastric mucosa (Ivy *et al.*, 1923; Palmer and Templeton, 1939; McKendry, 1950; McGeorge, 1950; Simon, 1949; Douglas *et al.*, 1950). Since the colon mucosa was known to be more sensitive to irradiation than the stomach (Regaud *et al.*, 1912; Lawrence and Tennant, 1937; Warren and Friedman, 1942), and the absorptive surface less deeply placed than the parietal cells, it was considered possible that colonic mucosal absorption might also be reduced by this means. Although much information was available on the histological appearances of the colon after irradiation (Bloom, 1948), the effect on its function of absorption was not known.

The aim of the present experiments was to study the absorption of chloride and sodium from colon loops and pouches before and after irradiation. Since it was hoped to reduce mucosal activity without interfering with motility, it seemed desirable to use intraluminal irradiation employing a beta-ray-emitting material which, having a low penetration, would affect mainly the mucosa. What was wanted was a radiocolloid of short half-life and high specific activity emitting energetic beta rays only and remaining essentially completely in the colon. Yttrium 90, with a half-life of sixty-six hours, and a maximum beta-energy of 2·24 MeV, was found to meet these requirements and was therefore used in these studies.

Since such intraluminal irradiation might interfere with colon motor activity, this was also measured in some of the absorption experiments by methods described elsewhere (Irvine *et al.*, 1961).

Experimental Plan and Materials

Using the radioisotope methods described below, the absorption of isotonic saline from canine colon before and after irradiation was studied in two groups of dogs. In the first group (9 dogs) a loop of lower colon was used with black silk serosal sutures to define its limits. The bowel was exposed on each occasion by open operation and each experiment was carried out under general anæsthesia. In the second group (4 dogs) an isolated colon pouch was prepared under strict aseptic conditions. This allowed repeated studies to be made under general anæsthesia without reopening the abdomen. Both animal preparations are illustrated in Fig. 1.

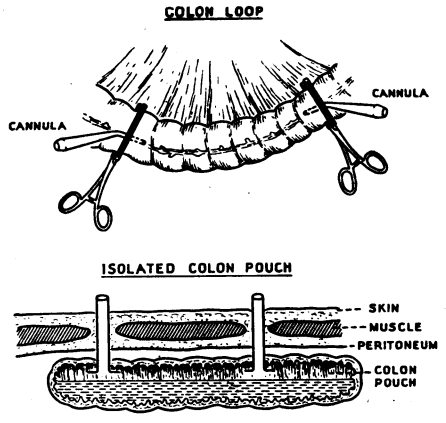

FIG. 1. — Diagrammatic representation showing method of isolating colon loop and anatomical arrangement in isolated colon pouches.

Isotope materials.—Radioactive chlorine 36 and sodium 24 were obtained from the Radiochemical Centre, Amersham. ^{24}Na (half-life fifteen hours, maximum gamma-ray energy 2·76 MeV, maximum beta-ray energy 1·39 MeV) was supplied as isotonic saline. ^{36}Cl (half-life $3{\cdot}1 \times 10^5$ years, maximum beta-ray energy 0·714 MeV) was delivered as 2N HCl, which was neutralized with sodium bicarbonate and made isotonic prior to use.

The yttrium preparation consisted of colloidal yttrium stabilized with dextran and irradiated with neutrons in a reactor. It was chosen after experiments had clearly indicated that it was not absorbed through the colon mucosa. It was specially prepared for this work by the staff of A.E.R.E., Harwell. Its main disadvantage, which will be further mentioned, was that it was strongly hypertonic.

Absorption methods.—Three tracer methods were used. In the first the rate of fall in ^{24}Na concentration in the isolated pouch was measured directly by means of a gamma-sensitive G-24Pb Geiger-Müller counter (20th Century Electronics) mounted over the pouch or loop containing the ^{24}Na solution; quantities of 100 μc were used for this purpose. The output from the Geiger-Müller tube was fed to an Ekco ratemeter type N.522A via a probe unit type 1014B and the fall in activity was recorded graphically against time on the recording ammeter (Evershed and Vignoles) linked in parallel with the ratemeter. By this means it was easy to observe the rate of removal of radioactivity from the colon lumen continuously throughout the experiment.

It was impossible to study chlorine transport by this method since the isotope used, which is the only feasible one, emits only beta rays.

A second source of information concerning ^{24}Na transport and also that of ^{36}Cl was obtained by aspiration of the lumen contents at the end of the absorption period. When measurements of ^{36}Cl transport were being carried out in this way 5 μc of ^{36}Cl was added to the experimental solution used in the colon. Several washings were normally required in order quantitatively to remove all radioactivity from the lumen. These were all pooled, the aspirate becoming diluted in the process to a volume of approximately 100 ml, this total volume being used for radioactive estimation of the contained ^{24}Na. The gamma-ray emission of an aliquot of the aspirate was measured by placing it in the centre of a ring of eight gamma-sensitive G.24Pb Geiger-Müller tubes connected in parallel. The count rate obtained from this aliquot was then compared with that of a standard prepared from a known volume of the original solution which had been retained before the experiment began. In this way the percentage of ^{24}Na remaining in the aspirate could be determined.

Thirdly, further measurements, made on the aliquot and standard after decay of ^{24}Na, could also be used for determination of the contained ^{36}Cl. For this purpose a beta-sensitive liquid counter type M.6 (20th Century Electronics) was used; and in practice it was usual to delay this measurement for fourteen days.

Technique of absorption studies.—The capacity of the surgically prepared loop or pouch was measured by determining the volume of physiological saline able to enter to a pressure of 5 cm saline. Absorption experiments were conducted after washing out the pouch or loop by instilling labelled physiological saline, the volume being equal to half of this measured capacity, which gave comfortable filling without distension, the hydrostatic pressure varying between 0·5 and 1·5 cm of saline.

In the loop preparations labelled isotonic saline was instilled via a cannula, the marked length of colon being temporarily isolated with non-crushing clamps. During the period of absorption the bowel and clamps were returned to the abdominal cavity. After an interval of 30 minutes, when approximately 50% of the sodium and chloride had been absorbed, the loop was completely aspirated, and the volume recorded. In many cases half of this initial aspirate was kept for chemical analysis. The loop was then irrigated three to four times with 20 ml of isotonic saline, the total aspirate being retained for subsequent determination of activity. The abdomen was then closed and each subsequent experiment in absorption required a further laparotomy. The same technique was followed each time, care being

taken to apply the clamps exactly opposite the marker sutures.

In the pouch preparations, after irrigation to remove mucus and instillation of the isotopes, a gamma-sensitive shielded G.24Pb counter was placed directly over the pouch, in contact with the surface of the abdomen, and the disappearance of activity recorded, as described, over thirty minutes. At the end of this period the pouch was aspirated and irrigated with isotonic saline to remove any remaining radioactive material; counting was then carried out as with the loops.

Control study with double colon loops.—In order to determine whether radioactive ions entering the blood stream and passing back into the colon loop contributed materially to the radioactivity remaining at the end of the 30-minute period, dogs were prepared with two separate colon pouches; into one was instilled isotope-labelled physiological saline and into the other ordinary physiological saline, under identical conditions. At the end of the 30-minute period the fall in radioactivity in the colon pouch with isotope-labelled saline was found to be associated with just detectable activity in the other. This activity accounted for less than 1% of the radioactive material in the pouch which had contained labelled ions. It was therefore concluded that reduction in isotope activity in the contents of the colon loops measured mainly unidirectional movement of labelled ions from the colon lumen into the blood stream.

Control studies using chemical and isotopic measurements of sodium and chloride.—In 3 of the dogs in this group chemical estimations of sodium and chloride were made from an aliquot of the removed fluid at the end of the absorption period.

Chemical methods.—Sodium was measured by the flame photometer and chloride by the Volhard-Harvey method (*see* Harvey, 1910).

These results made it clear that the measurement of disappearance of labelled ions from the colon lumen was not attended by the passage of unlabelled ions in the opposite direction to any marked extent. In short, the isotopic measurements of ions transport were essentially net absorption results.

Irradiation Methods Using Intact Colon Loops

(1) *Direct instillation of radioactive yttrium* 90.—The intact loop was prepared and cannulated as for an absorption experiment. Colloidal yttrium 90 was directly instilled until the loop was evenly distended. A statement of the activity of the preparation when leaving Harwell was supplied and, through knowledge of the half-life, the activity at the time of instillation could be calculated as described later, and from that the dose delivered to the mucosal surface in a finite time and at known volume.

The time required to give a specific dose was thus calculated and at the end of this period the active material was aspirated from the loop and the bowel irrigated to remove residual yttrium.

There were disadvantages to this technique. The yttrium 90 colloid was strongly hypertonic, which caused the fluid contained in the lumen of the bowel to increase in volume, thus diluting the irradiating solution. Despite this, the dose delivered could be subsequently calculated through measurement of the degree of dilution; but where this was appreciable the dose did not correspond with what had been planned. A further and more serious disadvantage was that the strongly hypertonic material often irritated the bowel and caused an increased secretion of mucus which, when present in quantity, reduced the effect of the irradiation in a manner which was quite indeterminable.

However, this was the only method which could be used for the isolated colon pouches.

(2) *Irradiation via an intraluminal balloon.*—A thin-walled cylindrical rubber balloon was constructed which, on distension, completely filled the colon loop, the mucosa lying in close and even apposition. The balloon was mounted on a central firm rubber tube, introduced via the anus, and manipulated into position at open operation. The balloon was filled with active material through a fine side channel, the dead space being reduced to just over 1 ml.

This method avoids the problems of dilution and mucus secretion, but a correction for beta-ray absorption by the balloon wall was necessary when calculating the dosage delivered.

(3) *Dosage calculations* are described elsewhere (Irvine *et al.*, 1961).

Histological Methods

After the final absorption study each dog was sacrificed, the colon loop or pouch removed for gross examination and then segments removed from the irradiated area and the untreated colon for histological study. Fixation was by 10% formalin and sections were stained by hæmatoxylin and eosin and cut 7 μ thick.

Results

The results can be considered in three separate groupings: first, the initial pilot studies in 4 dogs with loop preparations, where a high dose of irradiation proved that absorption could be reduced, but with resulting macroscopic damage to the colon and abnormal motility patterns. In the second group of loop studies smaller radiation

doses were used which again reduced absorption, without serious colon damage histologically and no evidence of impairment in motor activity. In the third group are the dogs with isolated colon pouches, allowing many more absorption studies to be made. These studies again confirmed inhibition of absorption without gross morphological damage.

Group I.—Heavily Irradiated Colon Loops

There were 4 dogs in this group. An initially high dose of irradiation (1,930–3,104 rads) was chosen to determine at the outset whether mucosal irradiation affected absorption to any significant extent. Base-line pre-irradiation absorption studies were restricted to two or three readings only and were repeated on only two occasions some three months after irradiation. At this time gross pathological changes were present in 3 of the 4 dogs, which were then sacrificed. In the fourth, since damage appeared minimal, studies were repeated after a further three months had elapsed. The results obtained are illustrated in Fig. 2.

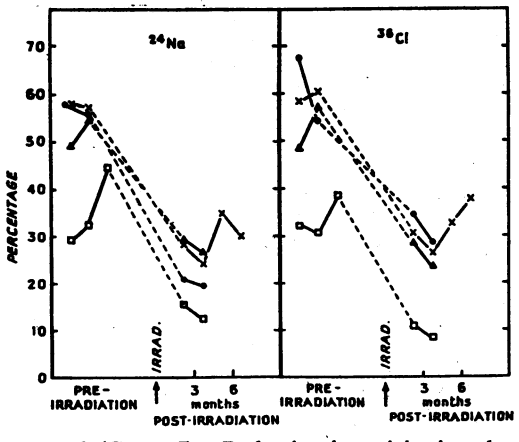

FIG. 2 (Group I).—Reduction in activity in colon lumen 30 minutes after instillation. Dosage to colon loop 2,000 to 3,000 r.

Pre-irradiation readings.—Absorption rates for both labelled ions were relatively constant in the individual animal and the standard deviations were small. However, there is variation in the absorption rates between one animal and another. In this group there is no statistically significant difference in the absorption of chlorine as compared with sodium.

Post-irradiation readings.—Three months after irradiation the absorption rates for both ions are approximately halved. The effect is not specific, both sodium and chlorine absorption being similarly reduced. The number of readings in the individual animals is too few for statistical analysis; but when they are considered as a group the reduction in absorption for both ions is separately significant, the probability being less than 0·5. In the one animal studied for six months there is a slight return towards pre-irradiation levels, but the reduction in absorption is still statistically significant.

Pathological findings.—Three of the four loops showed gross thickening of the wall of the colon loop and in two this thickening had produced some degree of stricture. Ulceration of the mucosa was frequently present. Histologically, the loss of colon epithelium with epithelial remnants regenerating, round cell infiltration of the submucosa and vasculitis were often seen (Fig. 3). Several dogs showed grossly abnormal motility patterns in this group.

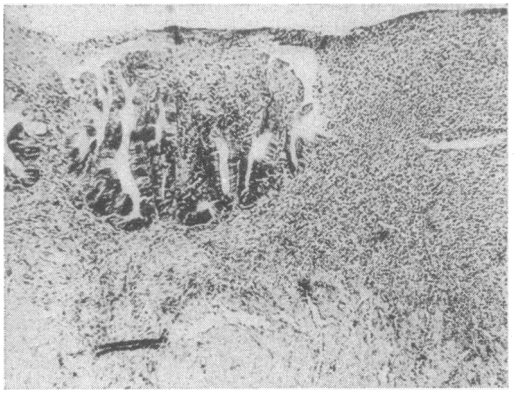

FIG. 3.—Effect of high dosage of irradiation on mucosa of colon loop.

Group II.—Colon Loops Receiving a Low Dose of Irradiation

The dose of irradiation was reduced to 750–1,220 rads in an attempt to reduce the injury to the bowel apparent in Group I. In all cases examination of the colon at three and six months after irradiation showed no significant macroscopical change in the irradiated segment. With one exception, all animals were studied for six months and at each period of the experiment a larger number of absorption readings was taken than in the first group. Fig. 4 shows the results.

Pre-irradiation readings.—Absorption rates for both ions in the individual animals are fairly constant and the standard deviations are smaller than in Group I. Again, there is quite wide variation in rate of electrolyte absorption between one animal and another. Taking this group as a whole, there is a greater absorption of chloride as compared with sodium, and this is statistically significant ($P<0·1$).

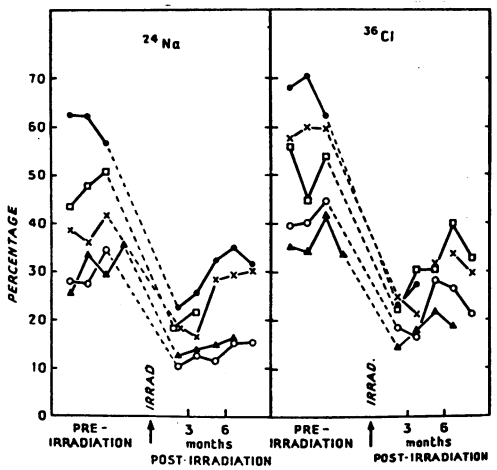

FIG. 4 (Group II).—Reduction in activity in colon lumen 30 minutes after instillation. Dosage to colon loop 750 to 1,220 rads.

Three-month post-irradiation readings.—Following irradiation, reductions in the rate of absorption for both ions are separately significant ($P<0{\cdot}5$) and in general the rates are 50% to 70% below the pre-irradiation levels. Despite the reduced dose of irradiation in this group, the effects on electrolyte absorption are no less marked than those seen in the heavily irradiated animals. The effect of irradiation is not specific, chloride and sodium absorption being similarly affected. The pattern of a slightly greater absorption of chloride as opposed to sodium, noted in the pre-irradiation readings, still persists after irradiation and is shown by all animals in the group.

Six-month post-irradiation readings.—In all animals there is a slight tendency for the absorption rates for both ions to increase towards their pre-irradiation levels, but at six months the reduced rates of absorption are still highly significant.

Pathological changes.—Macroscopically the 4 irradiated loops appeared normal. On inspection of the serosa, and when the loops were removed and opened, the mucosal surfaces showed no evidence of ulceration and the thickness of the bowel wall appeared normal. Microscopic examination revealed no gross abnormality (Fig. 5). The height of the epithelial cells may have been slightly reduced in one dog and in another a small area of submucosal fibrosis was seen. There were no abnormal mitoses.

Motility patterns were not altered by this dose of irradiation.

Group III.—Isolated Colon Pouches

There were 4 dogs in this group, two irradiated with 1,300 and two with 500 rads. The experimental data obtained in the isolated colon pouches are graphically recorded in Fig. 6.

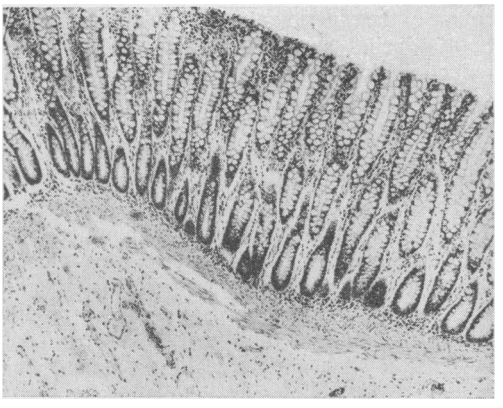

FIG. 5.—Effect of low dosage of irradiation on mucosa of colon loop.

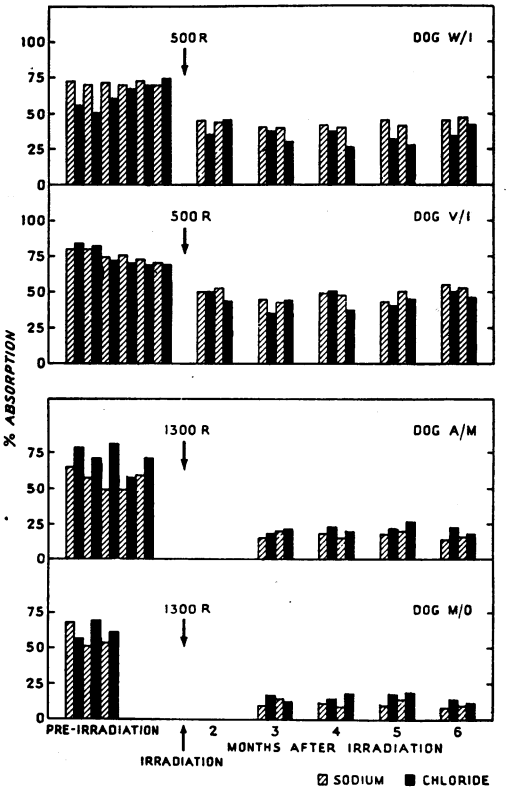

FIG. 6 (Group III).—Reduction in radioisotope activity in pouch lumen after 30 minutes.

Irradiation with 1,300 *rads.*—There is little individual variation between the two animals, but both show slightly greater absorption rates for chloride than sodium in the pre-irradiation period, and this is maintained throughout the

course of the experiment. Following irradiation, both pouches show a marked and sustained reduction in electrolyte absorption. This is apparent at three months and remains unchanged during the six months' experimental period. The effect is most marked in the second pouch, Dog M/O, where the fall in absorption rates for both ions is 70% to 80% below pre-irradiation levels. The fall in absorption rates for each ion is separately significant ($P<0{\cdot}1$). As in the intact colon loops, the effects are non-specific and both sodium and chloride absorption show proportional reductions. Both pouches show some evidence of slight histological damage and there is some reduction in pouch volume.

Irradiation with 500 rads.—Pre-irradiation absorption levels are similar in both animals. In contrast to the first two pouches, sodium absorption tends to run at a higher level than chloride. During the experiment the maximum effect on electrolyte absorption is apparent three months after irradiation, when the levels for both ions are approximately 40% below pre-irradiation readings. At six months there is a definite tendency to recovery in absorption rates, but this is slight and the reductions affected are still separately significant for each ion ($P<0{\cdot}1$).

The disappearance of labelled sodium as indicated by surface counting when plotted on semi-logarithmic paper against time produced a straight line which could be extrapolated to the theoretical time required for activity to be reduced 50%, assuming that the rate of absorption remained constant. This time interval significantly increased ($P<0{\cdot}01$) in each pouch after irradiation (Fig. 7).

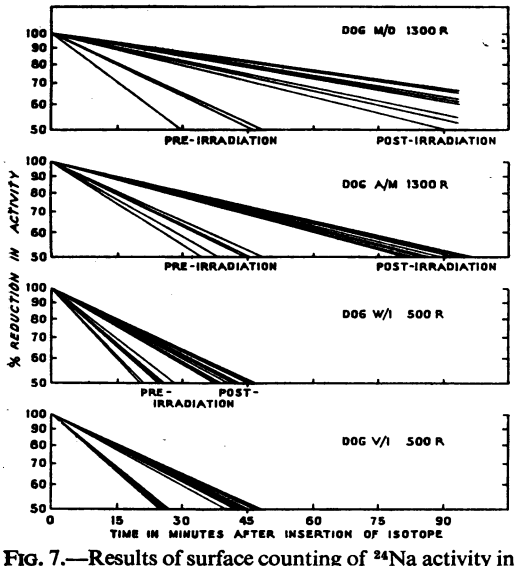

FIG. 7.—Results of surface counting of ^{24}Na activity in four pouches.

FIG. 8.—Effect of irradiation of mucosa on isolated colon pouch.

Pathological findings.—The pouches appeared macroscopically normal and histologically the walls of the pouches appeared normal. Fig. 8 represents the typical microscopic findings.

COMMENT

The isotope absorption studies reported here record mainly unidirectional movement of sodium and chloride ions from colon lumen to blood since experiments with double pouches showed clearly that less than 0·3% of the activity present in the lumen at the end of a half-hour period could be accounted for by backward movement of labelled ions into the colon lumen. The tests combining chemical and isotopic methods gave almost identical results in both pre- and post-irradiation states, allowing the conclusion that under the conditions of this study the unidirectional measurements closely approximated to the net absorption rate. Since pouch and loop volumes remained much the same before and after irradiation, especially in Groups II and III, comparisons of absorption rates before and after irradiation could be made.

In Groups II and III absorption rates were surprisingly constant for any individual animal, but there were wide variations within each group. Taking the pre-irradiation absorption results of each group as a whole, chloride appeared to be absorbed in excess of sodium in Groups II and III. In Group I there were fewer observations available for analysis and individual variations were much greater, perhaps because of imperfect techniques; but even in this group the overall picture is one of slightly greater chloride absorption, though it is not statistically significant. Larger periods of absorption may well have en-

hanced the difference between the amounts of chloride and sodium absorbed and in the ureterocolostomy patients many hours are available between voiding for reabsorption of the urinary constituents.

Intraluminal irradiation reduces significantly and equally the unidirectional movement of both sodium and chloride ions from colon to blood. At the higher doses of irradiation this is accompanied by gross morphological damage and evidence of motor dysfunction. At lower dosage this reduction of absorption can be produced without any evidence of histological damage and motor activity, as evidenced by the response to Prostigmin, appears the same. These studies suggest that it might be profitable to study experimentally the effect of intraluminal irradiation on the acidosis of ureteral transplantation. One possible side-effect of such treatment might be the effect of irradiation on potassium transport across the colon mucosa. Many ureterocolostomy patients are hypokalæmic and any increased loss of potassium would be serious. Such studies are at present in progress.

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Implantation of the Ureters into an Isolated Rectosigmoid Bladder

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PRIOR to 1950 the cause of the clinical failure, because of electrolyte imbalance, of some operations for ureterocolic anastomosis was not understood. In that year Ferris and Odel (1950) showed that hyperchloræmic acidosis develops following ureterocolic anastomosis in 75% of cases, but that in the majority of that 75% no clinical symptoms develop. A proportion of cases, a fifth to a quarter, however, do have symptoms of nausea, loss of appetite and a lack of the sense of well-being, and a still smaller proportion run into more dangerous symptoms, such as loss of weight, vomiting and sometimes coma and death. At first it was not understood how to deal with this chain of symptoms, which resulted partly from ascending renal infection from the colon to the kidneys and partly from the differential absorption of electrolytes from the colon, the acid chloride ions being absorbed in greater proportion than the basic sodium ions (Lapides, 1951; Parsons, Powell and Pyrah, 1952; Parsons, Pyrah, Powell, Reed and Spiers, 1952).

The disadvantages of ureterocolic anastomosis led to a search for alternative methods of urinary diversion, and the two principal ones which have been practised and advocated have been ileal ureterostomy, advocated first by Bricker (1950; Bricker *et al.*, 1954) and by Wells (1953, 1956), and the rectosigmoid bladder which I have advocated (Pyrah, 1956, 1957). The principle of these two operations is that the urine is deviated into a loop of intestine which is free from fæces, so that ascending renal infection is minimized.

The Rectosigmoid Bladder

In 1956 I reported to the British Association of Urological Surgeons 11 cases of rectosigmoid bladder with cystectomy (Pyrah, 1956) and the purpose of this communication is to bring the series up to date and to give the results. The procedure was first carried out by Mauclaire in 1895, but it was discarded.

Operation.—The operation has usually been carried out in two stages. The bowel is prepared by the administration of Aureomycin given orally. In the first stage, the sigmoid colon is divided transversely a little distance above the middle of the sigmoid loop, and the mesosigmoid including the marginal artery is divided at the line of section of the gut sufficiently deeply to allow the proximal end of the divided colon to be brought to the surface of the abdomen in the left iliac fossa without tension as an end-colostomy. The distal end of the sigmoid loop is infolded by two rows of catgut sutures. The new bladder then consists of the rectum and the lower half of the sigmoid colon. The left ureter is exposed and isolated at the outer side of the mesosigmoid