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Tumor induction and prophylaxis following different forms of intestinal urinary diversion in a rat model

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Abstract Eighty Wistar rats were randomized into two groups. In group 1 vesicosigmoidostomy with proximal colostomy was performed, in group 2, vesicosigmoidostomy. The total tumor incidence did not differ significantly (group 1 10/40, 25%; group 2 13/40, 32.5%). The tumor spectrum differed, with more adenocarcinomas in group 2 (11/40, 27.5% vs 4/40, 10%; $P = 0.047$) and urothelial carcinomas only in group 1 (5/40, 2.5%). One hundred and ten other Wistar rats were randomized into three groups. Animals in group A received vesicoileosigmoidostomy, group B, two-step vesicosigmoidostomy with initial separation of urine and the urocolonic anastomosis, group C, vesicosigmoidostomy. Significantly fewer adenocarcinomas were observed in group A (2/40, 5%) than in group B (16/40, 40%; $P < 0.002$) and group C (9/30, 30%; $P < 0.007$). These results indicate a similar cancer risk in all continent forms of urinary diversion, at least via colon. Ileal interposition seems to be an effective carcinoma prophylaxis following ureterosigmoidostomy. The proliferative instability at the urointestinal anastomosis is crucial for the pathogenesis and prophylaxis of this form of carcinogenesis, whereas urine seems to play only a minor role.

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At least 201 tumors following ureterosigmoidostomy have been reported in the world literature, leading many urologists to argue against this form of urinary diversion, especially for benign disease in younger patients [9, 12, 14]. This opinion was supported by Crissey, Steele and Gittes' basic experiments [2, 5] showing that the separation of feces and urine by a colostomy proximal to the vesicosigmoid anastomosis completely prevents adenocarcinoma following vesicosigmoidostomy in rats, compared to an incidence of 80% without such separation. On the other hand, however, there have been 34 case reports of tumors in urinary diversions via isolated intestinal segments such as cystoplasties, conduits of rectal bladders [7, 9]. The first part of the following experiments was designed to resolve this apparent contradiction.

Although 17 of the 34 tumors in isolated intestinal segments developed in ileal conduits or cystoplasties [7, 9], experimental data suggest that the increased cancer risk with intestino-intestinal anastomosis can be reduced or prevented by the use of ileum [4, 24]. The work of Roe et al. [18] and Strachan et al. [21] showed that there is proliferative instability during the first 3 months after intestino- or uro-intestinal anastomosis, with proliferation decreasing to normal thereafter. The second part of this study was intended to ascertain whether ileal interposition or the initial separation of the healing anastomosis and the potentially carcinogenic urine could decrease the cancer incidence following vesicosigmoidostomy in rats.

Materials and methods

Vesicosigmoidostomy with and without colostomy

80 female Hanover Wistar rats were prospectively randomized into two groups. The animals were operated according to the ureterosigmoidostomy model of Crissey et al. [2] and Gittes [5] with (group 1) and without colostomy (group 2) proximal to the vesicosigmoidostomy as described previously [2, 5, 8]. The animals of group 1 excreted urine only via the rectum. Nine rats that died within 5 months of surgery were replaced, yielding 80 eligible animals.

After 12 months the animals of both groups were killed and autopsied. The tumor incidences at the vesicocolonic anastomoses were compared using the exact Fisher test.

Two-step vesicosigmoidostomy and ileal interposition

One hundred and ten female Wistar rats were prospectively randomized into three groups. In group A ($n = 40$) a 5- to 7-mm-long ileal segment was isolated with intact blood supply and interposed between the bladder and the rectosigmoid, resulting in a vesicoileosigmoidostomy (Fig. 1). In group B ($n = 40$) a vescosigmoidostomy was performed, with the special feature that the urethra was left intact and the bladder dome was closed by running mattress sutures. Urine and feces thus remained separated, allowing the vesicosigmoid anastomosis to heal without contact with urine (Fig. 2a). Three months later the mattress suture line was excised, the urethra ligated and divided, and the bladder reanastomosed to the bladder patch already healed to the rectosigmoid (Fig. 2b). In group C ($n = 30$) a vesicosigmoidostomy was performed. Thirteen

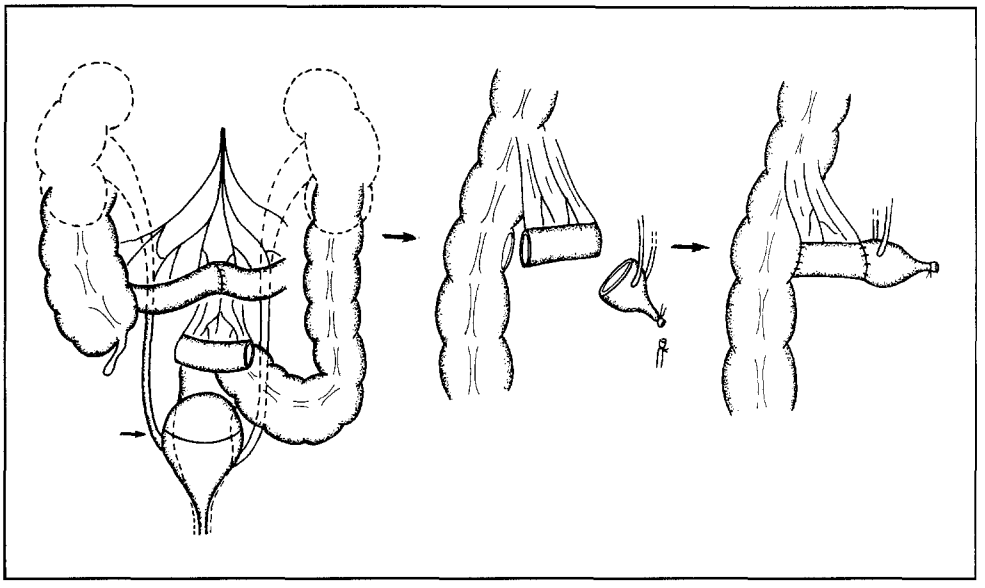

Fig. 1 Group A, vesicoileosigmoidostomy: Isolation of a 5- to 7-mm segment of ileum (*left*), ligation and division of urethra, resection of bladder dome, opening of anterior rectosigmoid (*middle*), end-to-end anastomosis of bladder/ileal segment, end-to-side anastomosis of ileal segment/rectosigmoid (*right*)

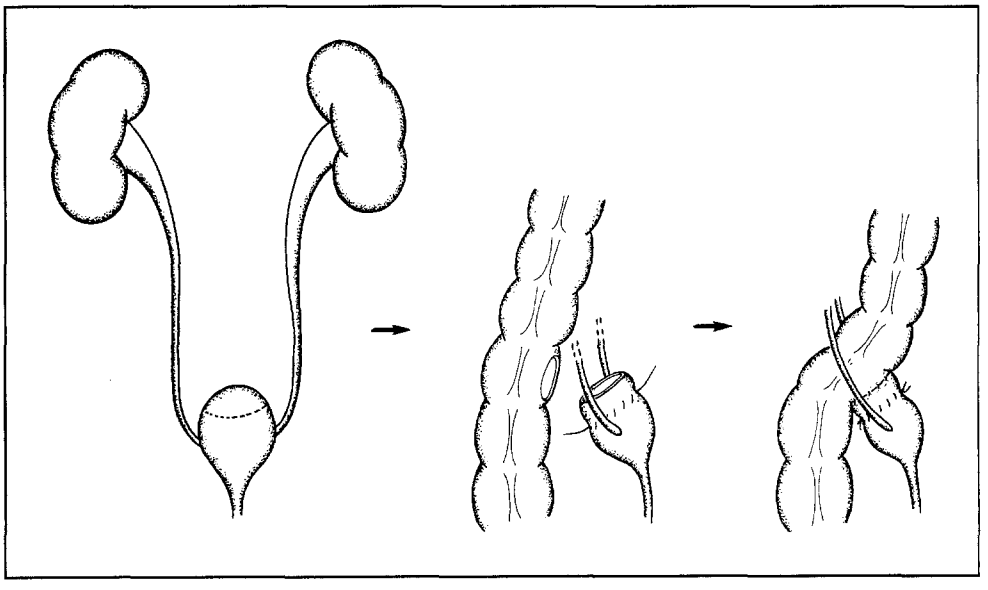

Fig. 2 a Group B, two-step vesicosigmoidostomy: *first step* Resection of bladder dome (*left*), closing mattress sutures through bladder dome separating urine from resection line (*middle*), end-to-side anastomosis of bladder/rectosigmoid (*right*).

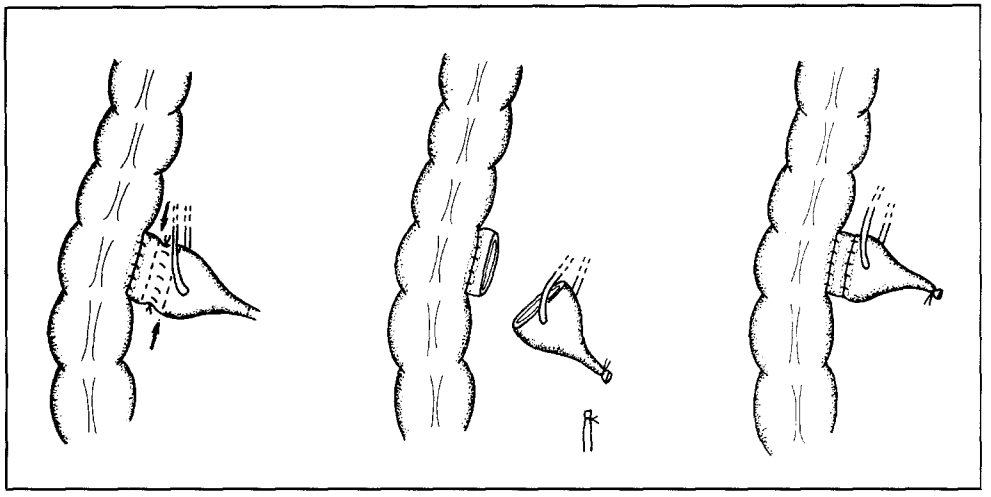

Fig. 2 b Group B, two-step vesicosigmoidostomy: *second step*. Resection of the mattress suture line (*left*), ligation and division of urethra (*middle*), end-to-end anastomosis of bladder/bladder patch at rectosigmoid (*right*)

animals that died within 5 months of surgery were replaced, yielding 110 eligible rats. Twelve months after operation in groups A and C and 15 months after the first operation in group B, the animals were killed and autopsied. The tumor incidences of the three groups were compared using the exact Fisher test.

Results

Vesicosigmoidostomy with and without colostomy

The tumors developing exactly at the vesicocolonic junction are presented in Table 1. The total incidence of adenomas, adenocarcinomas and urothelial carcinomas was not significantly different between group 1 (10/40, 25%) and group 2 (13/40, 32.5%). Both the number of adenocarcinomas and the combined number of adenomas and adenocarcinomas were significantly higher in group 2 (11/40, 27.5% and 13/40, 32.5%) than in group 1 [4/40, 10% ($P = 0.047$) and 5/40, 12.5% ($P = 0.017$)]. Urothelial carcinomas were observed only in group 1. The incidence of adenomas did not differ significantly between the two groups. All animals showed marked inflammatory hyperplastic changes with epithelial shifting between urothelium and colon epithelium. Two rats of group 1 had both a grade 2 adenocarcinoma and a grade 3 urothelial carcinoma. Two of 11 adenocarcinomas in group 2 showed secondary disease – one peritoneal carcinosis and one thymus gland metastasis.

Two-step vesicosigmoidostomy and ileal interposition

The tumors at the uro-intestinal anastomosis in the three groups are presented in Table 2. The incidence of adenocarcinomas in group A (vesico-ileosigmoidostomy; 2/40, 5%) was significantly lower than in group B (two-step vesicosigmoidostomy; 16/40, 40%; $P < 0.002$) and in group C (vesicosigmoidostomy; 9/30, 30%; $P < 0.007$). In group B, one urothelial carcinoma and one squamous cell carcinoma occurred, both growing close to a grade 1 adenocarcinoma. In contrast to the urothelial carcinomas and the adenocarcinomas, the squamous cell carcinoma grew outside the anastomosis at the bladder patch. The anastomotic regions in all three groups showed papillomatous hyperplasia with atypia and epithelial shifting.

Table 1 Tumors at the vesicocolonic anastomosis following vesicosigmoidostomy with (*group 1*) and without (*group 2*) proximal colostomy (*n.s.* not significant)

Tumor	Group 1 ($n = 40$)	Group 2 ($n = 40$)	P
Adenoma	1 (2.5%)	2 (5%)	n.s.
Adenocarcinoma	4 (10%)	11 (27.5%)	0.047
Urothelial carcinoma	5 (12.5%)	0	0.022
Total	10 (25%)	13 (32.5%)	n.s.

Table 2 Tumors at the vesicocolonic anastomosis following vesico-ileosigmoidostomy (*group A*) two-step vesicosigmoidostomy (*group B*) and vesicosigmoidostomy (*group C*)

Tumor	Group A ($n = 40$)	Group B ($n = 40$)	Group C ($n = 30$)
Adenocarcinoma	2 (5%)	16 (40%)	9 (30%)
Urothelial carcinoma	–	1 (2.5%)	–
Squamous cell carcinoma	–	1 (32.5%)	–

Discussion

The renaissance of ureterosigmoidostomy in the 1960s and 1970s was followed by reports of increasing numbers of tumors arising at the urocolonic borderline. To

the best of our knowledge, to date 201 adenomas, juvenile polyps, urothelial carcinomas and adenocarcinomas have been reported so far [9, 12, 14]. The conclusion that ureterosigmoidostomy should be abandoned on the face of this serious threat is challenged by the 34 tumors reported in intestinal urinary diversions without feces (Table 3), 9 occurring in colocystoplasties and 10 in ileocystoplasties. The histology, the localization and the mean latency periods of these tumors are similar to those following ureterosigmoidostomy. Taking into account the fact that ureterosigmoidostomy has been used worldwide since 1911, with a very broad spectrum of indications, whereas cystoplasties have been performed only since the late 1950s with comparatively few indications, the cancer risk seems similar in all continent forms of urinary diversion using ileum or colon, with and without separation of feces and urine. This cannot be stated with confidence, however, due to the long latency period, the unknown number of urinary diversions performed and the unknown number of unreported tumors. Apart from that, the tumor risk in pouches and neobladders will not become clear until at least 30 years from now.

For these reasons, animal experiments seem to be the only way to elucidate this field. Crissey, Steele and Gittes' pioneer work [2, 5] showed that an animal model for ureterosigmoidostomy well simulates the situation in humans in the short time of about 1 year. Their widely accepted finding of tumor prevention by separation of feces and urine does not, however, correlate with the other clinical data mentioned above. We therefore compared vesicosigmoidostomy in rats with and without colostomy, simulating both ureterosigmoidostomy and rectal bladder. The total tumor incidence (Table 1) did not differ significantly, indicating a similar cancer risk in all continent forms of urinary diversion, at least via the colon. Miersch and Vogel, [15] using microsurgical methods, found similar tumor frequencies in rats with rectal bladders (25%) and ureterosigmoidostomies (28.5%). The reports of 10 tumors in ileocystoplasties (Table 3) compared to 9 in colocystoplasties suggest, in addition, a comparable cancer risk in all continent intestinal urinary reservoirs using colon or ileum. Crissey and Gittes' results [2, 5] could not be confirmed.

Table 3 Summary of case reports of tumors following urinary diversion using isolated intestinal segments without feces

Operation	Median (range) latency period, months	Ileum (*n*)	Colon (*n*)	Total (*n*)
Cystoplasty	21 (7–30)	10	–	
	15 (0.3–24)	–	9	19
Rectal bladder	16 (11–28)	–	3	3
Colon bladder	0.3	–	1	1
Conduit	16 (5–22)	7	4	11
Total	17 (1–25)	17	17	34

The tumor spectrum, however, differed significantly between the two groups, with a predominance of urothelial carcinomas in group 1 (Table 1). The reason for this is unclear, but it is in accordance both with Miersch and Vogel's experimental results [15] and with the fact that 4 of the 19 tumors in cystoplasties [7, 9] were of urothelial origin, but only 1 of the 201 tumors after ureterosigmoidostomies. Perhaps the risk of urothelial carcinoma is slightly higher in urinary diversions without feces.

In any case, both epithelia at the urocolonic anastomosis showed marked proliferation, with induction of adenocarcinoma and urothelial carcinoma at the same vesicocolonic anastomosis in three animals. Gregoire et al. observed a synchronous transitional carcinoma and adenocarcinoma in a cecocystoplasty [6].

Strachan et al. [21] found increased crypt cell production rates at urocolonic anastomoses in rats with and without urine/feces mixture. Roe et al. [18] observed increased crypt cell proliferation at experimental colon anastomoses which returned to normal values 12 weeks after operation. Taking into account the fact that urine contains epidermal growth factor (EGF) and EGF-related growth factors able to increase bladder cancer growth [26], our hypothesis was that the combination of urine and the unstable proliferation during the first 3 months after surgery could be of importance for carcinogenesis following urinary diversion.

Therefore we separated the anastomosis from urine during the first 12 weeks after vesicosigmoidostomy with the aim of preventing tumor growth. Surprisingly, the adenocarcinoma incidence was higher than with common vesicosigmoidostomy (16/40, 40% vs 9/30, 30%). Although the difference was not statistically significant, the finding that two operations adjacent to the urocolonic anastomosis appear to increase the tumor risk emphasizes the importance of the proliferative potency of the anastomosis itself for this form of carcinogenesis. Urine seems to play only a minor role; otherwise, the initial separation of urine from the healing anastomosis would have reduced cancer risk.

Although the clinical data suggest a similar cancer risk in continent urinary diversions using colon and ileum, Gennaro et al. [4] and Williamson et al. [24] found lower tumor incidence in transposed ileal segments and at ileocolonic anastomoses than in transposed colonic segments and at colocolonic anastomoses following administration of colon carcinogens in rats. In accordance with these findings, Gittes [5] mentioned that ileum interposition seemed to protect against tumor growth following vesicosigmoidostomy. As described above, we achieved a significant reduction in the incidence of adenocarcinomas, from 30% to 5% ($P < 0.007$), of a small ileal segment between bladder and rectosigmoid. These results suggest a protective role of any form of ileal interposition between ureter and sigmoid colon in ureterosigmoidostomies in humans, for example a Hemi-Kock

procedure [13] or an ileocecal segment [10]. These results may even imply lower tumor risk in continent pouches and neobladders using ileum alone, despite the similar number of tumor reports in ileo- and colocystoplasties.

On the other hand, vesicoileosigmoidostomy is not a correct model for an ileocystoplasty or an ileal neobladder. The published results of animal experiments with ileo-or colostoplasties are difficult to interpret. Young et al. [25] found a 13% and 15% incidence of papillary lesions in ileo- and sigmoidocystoplasties respectively, in rats. Although they classified these neoplasms as benign, they found them similar to the tumors following vesicosigmoidostomy in the literature, thus indicating a similar cancer risk in both forms of cystoplasty. Spencer et al. [20] observed one urothelial carcinoma and a number of hyperplastic lesions both in ileo- and in colocystoplasty. Because of the lack of adenocarcinomas they described the rat model as not ideal, although the lesions were at the urointestinal anastomoses and an accumulation of urothelial carcinomas in urinary diversions without feces is common both in rats [15] and in humans [7,9]. It seems necessary to carry out further research on cystoplasties in rats, involving pathologists accustomed to evaluating specimens with marked inflammatory artifacts in order to obtain comparable results for all forms of urinary diversion. Daher et al. [3], for example, reported that five pathologists interpreting vesicosigmoidostomy specimens found different numbers of adenocarcinomas, varying from none to seven. Therefore, it could well be that other pathologists would have classified Young et al.'s [25] lesions as malignant.

In conclusion, the cancer risk in different forms of intestinal urinary diversions including pouches and orthotopic neobladders, will not be able to be estimated from for at least 30–50 years from now. The available experimental data [15] suggest a similar tumor risk in ureterosigmoidostomies and colon pouches or neobladders (Indiana, Mainz). The exact assessment of the risk in ileal neobladders (Hautmann) compared to colonic pouches is not yet possible.

Concerning the etiology of the tumors it is clear that proliferative instability at the urointestinal borderline [15,18,21] is the most important cause. Wound macrophages expressing growth factors [16] may play an additive role. Gregoire et al. [6] speculate that the mutation of oncogenes could also be of importance [19]. Prostaglandins known to affect cell proliferation and tumor growth [17], as well as ornithine decarboxylase (ODC), the key enzyme of polyamine synthesis [11,23] may be important mediators. Constituents of urine, however, especially urinary carcinogens such as nitrosamines, play only a minor role in this form of carcinogenesis [8].

The key measure in tumor prophylaxis, then, is modification of the instability of the urointestinal anastomosis. Although ileal interposition promises reduction – not complete prevention – of tumors following ureterosigmoidostomy, routine use in clinical practice does not seem worthwhile due to the increased surgical complications. A very promising form of prophylaxis, however, is the administration of non-steroidal antiinflammatory drugs (NSAIDs) and difluoromethylornithine to inhibit the synthesis of prostaglandins and ODC, respectively. Both drugs reduced colon cancer rate in experimental animals [11,17,22]. Furthermore, epidemiological data suggest a prophylactic effect of aspirin, an NSAID, in colon cancer of humans [22]. Surgical prophylaxis, using reverse intestinal seromuscular enterocystoplasty in order to avoid urointestinal anastomosis, may also be of value [1].

In any case, further research into prophylaxis and etiology, as well as the reporting of all tumors following urinary diversion, is necessary to enable selection of the reservoirs associated with the fewest and least severe complications and the lowest risk of tumor induction.

References

1. Badiola F, Manivel CJ, Gonzalez R (1991) Seromuscular enterocystoplasty in rats. J. Urol 146:559
2. Crissey MM, Steele GD, Gittes RF (1980) Rat model for carcinogenesis in ureterosigmoidostomy. Science 207:1079
3. Daher N, Gautier R, Abourachid H, Decaens C, Bara J (1988) Rat colonic carcinogenesis after ureterosigmoidostomy: pathogenesis and immunohistological study. J Urol 139:1331
4. Gennaro AR, Villanueva R, Sukonthaman Y, Vathanophas V, Rosemond GP (1973) Chemical carcinogenesis in transposed intestinal segments. Cancer Res 33:536
5. Gittes RF (1986) Carcinogenesis in ureterosigmoidostomy. Urol Clin North Am 13:201
6. Gregoire M, Kantoff P, DeWolf CW (1993) Synchronous adenocarcinoma and transitional cell carcinoma of the bladder associated with augmentation: case report and review of the literature. J Urol 149:115
7. Kälble T (1993) The risk of malignancy after cystoplasty. Cur Opin Urol 3:476
8. Kälble T, Tricker AR, Berger M, Amelung R, Waldherr R, Hothorn L, Möhring K, Staehler G (1991) Tumor induction in a rat model for ureterosigmoidostomy without evidence of nitrosamine formation. J Urol 146:862
9. Kälble T, Schreiber W, Berger MR, Waldherr R, Amelung F, Möhring K, Staehler G (1993) Risk of carcinoma in different forms of urinary diversion via intestine. Aktnelle Urol 24:1
10. Kim KS, Susskind MR, King LR (1988) Ileocecal ureterosigmoidostomy: an alternative to conventional ureterosigmoidostomy. J Urol 140:1494
11. Kingsnorth AN, King WK, Diekema KA, McCann PP, Ross JS, Malt RA (1983) Inhibition of ornithine decarboxylase with 2-difluoromethylornithine: reduced incidence of dimethylhydrazine-induced colon tumors in mice. Cancer Res 43:2545
12. Kliment J, Luptak J, Lofaj M, Horakova M, Beseda A (1993) Carcinoma of the colon after ureterosigmoidostomy and trigonosigmoidostomy for exstrophy of the bladder. Int Urol Nephrol 25:339
13. Kock GN, Mohamed AG, Lycke GK, Mahran RM (1988) Urinary diversion to the augmented and valved rectum: preliminary results with a novel surgical procedure. J Urol 140:1375
14. Marino BM, Vitale L, Kiss A, Rossi R, Drago GW (1994) Carcinoma of the large intestine following ureterosigmoidostomy in a patient with bladder exstrophy. Minerva Chir 49

15. Miersch WDE, Vogel J (1992) Induction of carcinoma at ureterosigmoid anastomosis – with and without faecal stream. Br J Urol 69:499
16. Rappolee AD, Mark D, Banda MJ, Werb Z (1988) Wound macrophages express TGF-alpha and other growth factors in vivo: analysis by mRNA phenotyping. Science 242:708
17. Reddy SB, Tokumo K, Kulkarni N, Aligia C, Kelloff G (1992) Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. Carcinogenesis 13:1019
18. Roe R, Fermor B, Williamson RCN (1987) Proliferative instability and experimental carcinogenesis at colonic anastomoses. Gut 28:808
19. Schuh AC, Keating J, Monteclaro FS, Vogt PK, Breitman ML (1990) Obligatory wounding requirement for tumorigenesis in v-*jun* transgenic mice. Nature 346:756
20. Spencer JR, Steckel J, May M, Marion D, Hernandez K, Vaughan ED Jr (1993) Histological and bacteriological findings in long-term ileocystoplasty and colocystoplasty in the rat. J Urol 150:1321
21. Strachan JR, Matthews J, Rees HC, Cooke T (1987) Kinetic changes in experimental colonic urinary diversion. Br J Surg 74:1046
22. Thun MJ, Mohan MD, Namboodiri M, Heath C Jr (1991) Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 325:1593
23. Weber TR, Westfall SH, Steinhardt GF, Webb L, Avila CS, Conners RH (1988) Malignancy associated with ureterosigmoidostomy: detection by mucosa ornithine decarboxylase. J. Pediatr Surg 23:1091
24. Williamson RCN, Davies PW, Bristol JB, Wells M (1992) Intestinal adaptation and experimental carcinogenesis after partial colectomy. Gut 23:316
25. Young PR, Kreder KJ, Akwari O, Godfried M, Webster GD, Durham NC (1993) Carcinogenic potential in augmented bladders: a rat model. J. Urol 149:373A
26. Yura Y, Hayashi O, Kelly M, Oyasu R (1989) Identification of epidermal growth factor as a compenent of the rat urinary bladder tumor-enhancing urinary fractions. Cancer Res 49:1548