

achieved simply by stopping therapy until symptoms subside—usually in four to five days—and then resuming therapy gradually with increasing doses over several weeks. We have used D-pen. successfully now in two patients with well-documented histories of penicillin allergy.

Previously it was our belief that D-pen. would be effective only in preventing *de novo* stone formation or progression of stones already formed. Therefore patients with calculi and pyelonephritis—a complication we not infrequently encountered—were rendered stone-free surgically in order to maximize chances for eradicating infection with selected antibiotics. Our success in dissolving stones in each of these four patients has led us now to be more conservative in recommending operation to patients with nephrolithiasis complicated by pyelonephritis.

So far we have not encountered any patient whose stones proved refractory to dissolution when D-pen. was added to the conventional programme.

Over the last two years five of our patients have decided, quite against our advice, to omit fluids, alkali, and methionine restriction and to continue only on D-pen. All have remained stone-free.

Because D-pen. is thought to suppress cystine most successfully in an alkaline urine we have been hesitant previously to acidify the urine of patients infected with *Proteus vulgaris* or patients in whom long-term suppressive therapy with Mandelamine was indicated. Our experience in Case 2 indicates that high-acidity of the urine does not interfere with the action of D-pen. Our plan with this patient is to dissolve the stones

completely and then attempt a cure of pyelonephritis with appropriate antibiotics.

### Summary

Significant stone dissolution occurred in four patients with cystine calculi when D-penicillamine was added to a previously ineffective conventional therapeutic programme of forced fluids, alkali, and in three cases methionine restriction.

Elective surgery for refractory nephrolithiasis complicated by pyelonephritis should be deferred until a reasonable trial has been made to effect stone dissolution with D-penicillamine.

D-Penicillamine is a highly effective therapeutic agent in cystinuria even when used alone in the absence of the conventional programme.

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## Small-bowel Ulceration Induced by Potassium Chloride

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Sporadic cases have been reported from time to time of non-specific ulceration of the small intestine presenting as intestinal obstruction, perforation, or haemorrhage. Recently it has become recognized that a stenosing ulcer of the small intestine may develop as a rare complication of medication with enteric-coated diuretic and potassium chloride tablets.

We report six further cases. All our patients had been taking Hydrosaluric-K (enteric-coated hydrochlorothiazide with potassium chloride). One patient had taken only two tablets. We think it important that the condition be recognized as a cause of intestinal obstruction and perforation in patients taking these preparations. If the symptoms are recognized early enough improvement may follow cessation of treatment.

### Case 1

A man aged 54 was admitted to hospital on 25 May 1964 with a 12-hour history of central abdominal colicky pain and vomiting. For two months he had experienced attacks of abdominal pain, usually occurring one hour after meals. He had been under treatment for malignant hypertension for five years, and had suffered a coronary thrombosis seven months previously. Gastrografin x-ray

studies of the small intestine supported a diagnosis of small-intestine obstruction, and laparotomy was advised. At operation on 27 May distended small intestine was traced down to a stricture in the distal ileum. The bowel was collapsed beyond this point. The stricture had the appearance of a smooth ring of narrowing 1–2 mm. wide in the wall of the ileum, and causing almost complete occlusion of the lumen. There was no abnormality in the mesentery, and normal pulsation was observed in the vessels locally supplying the intestine. The stricture was thought to be benign, and, in view of the anaesthetic risk involved, the operation was limited to an entero-anastomosis bypassing the stricture. The patient has had no further attacks of abdominal pain since his discharge from hospital, and has started light work.

Since the diagnosis of malignant hypertension in 1960 this patient has been treated mainly with Inversine (mecamylamine) and Saluric (chlorothiazide). The Saluric was discontinued in favour of Hydrosaluric-K in 1962, and he had been taking two tablets a day, three days a week. He had also been given Darenthin (bretylum tosylate), Serpasil (reserpine), guanethidine, pyridostigmine, and neostigmine for short periods.

### Case 2

A man aged 49 was admitted to hospital on 15 October 1964 with a two-day history of increasingly severe abdominal pain, vomiting, and diarrhoea. He had been admitted to hospital five years, six months, and two months previously on account of abdominal pain,

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diagnosed as diverticulitis, and had been treated. There was also a history of repeated haemoptyses from mitral stenosis, for which mitral valvotomy was performed six years previously; and he suffered from asthma and hay-fever. He had been admitted to hospital two or three times a year since the mitral valvotomy on account of congestive cardiac failure, and had been unfit for work for the past five years. This history was subsequently compiled from hospital notes.

On admission he was too ill to give a satisfactory history. He was breathless even when sitting, was cyanosed, and had auricular fibrillation. The abdomen was distended, tender, and tympanitic. Straight x-ray films of the abdomen supported the diagnosis of intestinal obstruction, and operation was thought to be urgent, particularly as the abdominal distension was contributing to the cardio-respiratory embarrassment. Laparotomy revealed a thick fibrous ring in the wall of the ileum, about 75 cm. from the ileo-caecal valve, almost occluding the lumen and with distension of the proximal small intestine. The bowel was opened at the site of the stricture by a longitudinal incision. The narrowing seemed to be due to a sub-mucosal fibrous stricture 2 mm. wide, and the mucosa appeared to be congested but intact. The enterotomy was sutured transversely, relieving the stricture. The presence of diverticulosis of the pelvic colon was confirmed. Convalescence was complicated by strangulated haemorrhoids, but was otherwise uneventful. He has since been readmitted on three occasions with congestive cardiac failure, and has had one attack of lower abdominal pain and vomiting, which settled.

It should be mentioned that at the time of his admission with abdominal pain in 1959 there was a tender mass in the left side of the pelvis. Later, barium enema x-ray studies supported the diagnosis of diverticulitis. The two more recent episodes of abdominal pain seem, in retrospect, to have probably been caused by the small-bowel stenosis.

In the six years prior to developing small-bowel stenosis this patient was treated with: Saluric, 1 g. daily twice a week; potassium chloride, 0.5 g. t.d.s. for the first three and a half years; and Hydrosaluric-K, two tablets on three days a week for one and a half years. He was also treated intermittently with digoxin, quinidine, Cedilanid (lanatoside C), Cholestyl (choline theophyllinate), and antibiotics.

Hydrosaluric-K, one tablet t.d.s. on alternate days, was continued post-operatively until February 1965, when Centyl-K (bendrofluazide) was given in a dosage of two tablets on alternate days.

### Case 3

A man aged 50 was admitted to hospital on 11 August 1963 complaining of central abdominal colic, which had occurred intermittently over a period of approximately six weeks. The pain was often followed by nausea and vomiting. He had repeatedly been admitted to hospital previously on account of three severe attacks of coronary thrombosis in five years, and a carotid artery thrombosis. His most recent coronary thrombosis was 13 months prior to admission. Examination revealed a slightly distended abdomen, over-active bowel sounds, but no localized tenderness. There was considerable left ventricular enlargement, and his blood-pressure was 140/85. The description of the pain and his appearance were typical of a subacute obstructive lesion of the small bowel. A straight abdominal x-ray examination on 13 August was unhelpful, and did not reveal any significant small-bowel obstruction.

At laparotomy on 16 August evidence of small-bowel obstruction was found. A stricture was present 100 cm. proximal to the ileo-caecal angle. The mesenteric vessels appeared to be normal, and there was no glandular enlargement. The stricture was resected and an end-to-end anastomosis carried out. Further examination revealed another stricture 150 cm. proximal to this one; the narrowing was not so great and intestinal hold-up was minimal. This stricture was bypassed by entero-anastomosis. Examination of the resected bowel revealed a circumferential constricting ulcer 5 mm. wide. Microscopically a non-specific inflammatory reaction with ulceration and submucosal fibrosis was present without any apparent vascular or lymphatic changes.

A smooth recovery followed the operation, and the patient continued to make satisfactory progress for approximately eight months. He then started to complain of further attacks of abdominal pain associated with vomiting, occasional diarrhoea, and distension of the

abdomen. These attacks of pain continued for three months. He volunteered the information that the abdominal pains became worse or were precipitated some three to four hours after taking the tablets. He had noted a clear association with this drug because it was taken on alternate days, and he asked his general practitioner if these tablets could be discontinued. Since discontinuing the Hydrosaluric-K he has had mild attacks of colic, but they have been less frequent and less troublesome. He had a barium-meal and follow-through examination as an in-patient on 17 June 1965; this showed no evidence of obstruction.

He had been taking Hydrosaluric-K, two tablets daily, for over 12 months, and had also been treated with Librium (chlorodiazepoxide hydrochloride), Dindevan (phenindione), and digoxin. Therapy with Hydrosaluric-K was stopped during the period of operation, but just prior to discharge the above regimen was continued, but the dose of diuretic was reduced to one tablet on alternate days. Diuretic therapy was stopped at the end of January 1965.

### Case 4

A man aged 72 was admitted to hospital on 27 June 1965 because of the sudden onset of severe lower abdominal pain a few hours previously. He denied any previous abdominal pain, though he was known to have cholelithiasis. He had suffered from chronic bronchitis and emphysema for many years, and had recently recovered from an attack of left ventricular cardiac failure. He was not hypertensive. Electrocardiography showed evidence of myocardial ischaemia.

Examination revealed generalized abdominal tenderness and rigidity compatible with peritonitis, and an emergency operation was performed. Laparotomy revealed a foul-smelling peritoneal exudate with a 5-mm. perforation in the small bowel 60 cm. proximal to the ileo-caecal angle. No other lesion was apparent in the alimentary tract. The perforated segment of ileum was resected and intestinal continuity restored by end-to-end anastomosis. The patient made a good recovery from the operation, but convalescence was delayed by respiratory complications. Examination of the resected bowel showed that the perforation had occurred in a circumferential ulcer, and microscopically the ulceration showed acute non-specific inflammatory reaction involving all coats in its deepest parts.

During the past two years the patient had been treated with digoxin, and, for the past 12 months, with Hydrosaluric-K, two tablets a day, morning and evening, half an hour before meals. A tablet had been taken six hours prior to the symptoms of perforation.

### Case 5

A spinster aged 62 was admitted to hospital on 24 June 1965 with a three-month history of attacks of central abdominal colicky pain associated with borborygmi and occasional vomiting. She was known to have a right renal calculus, and a left femoral hernia had been repaired six weeks previously. At this operation a fatty protrusion was found, but no sac. Two barium-meal x-ray studies of the small intestine and a barium enema had been carried out in the previous two months and had shown no abnormality, except for a solitary diverticulum of the pelvic colon. Sigmoidoscopy had not revealed any abnormality. She suffered from hypertension and had been treated with Aldomet (methyldopa) one tablet t.d.s. for the previous 12 months, and intermittently with Hydrosaluric-K, one tablet b.d. on three days a week.

At laparotomy on 29 June a fibrous stricture near the midpoint of the small intestine was found. The stricture would admit only the tip of the little finger. Proximal to the stricture 12 in. (30 cm.) of bowel was dilated and distally the bowel was collapsed. The stricture was resected, with restoration of alimentary continuity by end-to-end anastomosis.

Convalescence was uneventful, and the patient was discharged from hospital 15 days post-operatively.

Histological examination of the specimen revealed that the stricture was mostly mucosal with some degree of chronic inflammatory infiltration but without ulceration. From the histological appearances the pathologist favoured a congenital origin. We think that from the history and clinical resemblance to our other cases the stricture was probably due to the healing of a circumferential ulcer.

### Case 6

A man aged 56 was admitted to hospital on 4 July 1965. He gave a three-week history of colicky central abdominal pain, diarrhoea, and occasional vomiting. The pain had become more severe on the day of his admission to hospital. On examination he had a distended abdomen. The pulse was regular and 90/minute and the blood-pressure 170/100 mm. Hg. The heart was moderately enlarged, and there was no peripheral oedema. Straight x-ray films of the abdomen supported a diagnosis of small-bowel obstruction. A history of medication with Hydrosaluric-K was obtained, and a tentative diagnosis of stenosing ulcer was made. Laparotomy was performed that evening, and the obstruction was found to be due to a stricture of the proximal ileum. The small bowel was distended above this point and collapsed distally. Twelve centimetres of small intestine containing the stricture was resected and continuity restored by an end-to-end anastomosis. Recovery was uneventful, and the patient was discharged from hospital on the twelfth post-operative day.

Examination of the specimen revealed a stenosing circumferential ulcer 5 mm. wide. The gut was narrowed to the diameter of a goose quill at this point, and on section there was extensive submucosal non-specific inflammatory infiltration.

For about a year the patient had been taking preparations of digoxin for dyspnoea of cardiac origin. At about the time he started to suffer from colic he had been prescribed Hydrosaluric-K for oedema of the legs, but had not taken more than two tablets, because he blamed the tablets for his abdominal symptoms.

### Discussion

Prior to 1963 ulceration of the small intestine seems to have been a rare condition, only 170 cases having been published in the world literature (Watson, 1963). Since then five papers (Baker *et al.*, 1964; Lindholmer *et al.*, 1964; Buchan and Houston, 1965; Morgenstern *et al.*, 1965; Abbruzzese and Gooding, 1965) have added a further 53 cases, in which 48 patients had been taking enteric-coated thiazide and potassium chloride tablets, three patients may have been, and two had not. Our experience agrees with that of Morgenstern *et al.* (1965) that the pathology of the lesion is a distinct entity with naked-eye appearances of "a sharply delineated zone of cicatricial narrowing, producing incomplete, or near complete, obstruction."

The histology of the lesion has usually been a circumferential stenosing ulcer with a band of submucosal inflammation and fibrosis, but there was no ulceration at the time of operation in one of the cases of Baker *et al.* (1964), as in two of our patients. Most of the patients presented with intestinal obstruction, and seven of the reported cases and one of ours presented as a perforation of the intestine (Baker *et al.*, 1964; Morgenstern *et al.*, 1965).

The site of the lesion has been about equally distributed between jejunum and ileum. In most cases the lesion has been solitary, but in three previously recorded cases and in one of this series the lesion has been double. In Case 6 the patient took only two Hydrosaluric-K tablets. Nevertheless, it would appear that ulceration can occur after such small dosage (Boley *et al.*, 1965), and this is supported by the animal experimental evidence.

There has been much speculation on the cause of the lesion. Baker *et al.* thought that the combination of these ingredients (a diuretic with potassium chloride) in the presence of cardiovascular disease may be the cause, as all their patients (12), as in ours, had cardiovascular disease in varying degrees. However, 2 of the 17 cases reported by Morgenstern *et al.*, and three cases of Buchan and Houston's, were receiving these drugs for reasons other than severe cardiovascular disease. It is of interest that a recognizable pill was found near the site of the lesion in one of Baker's cases. Buchan and Houston give interesting details of the composition of the pill. Some preparations consist of an enteric-coated mixture of thiazide with potassium chloride,

while in other preparations the potassium chloride is in an enteric-coated core. Cases have been reported after medication with both types of preparation. These authors also give details of the enteric coat, and suggest that the diethyl phthalate used may be irritating to mucous membranes. Nine of Baker's 11 cases had been taking Esidrix-K,<sup>1</sup> which contains 1 g. of potassium chloride, compared with the 572–600 mg. of most other preparations.

Lawrason *et al.* (1965), in a preliminary report of their animal investigations, state that commercially available enteric-coated tablets of diuretics in combination with potassium chloride readily produced ulcerative lesions of the small intestines of monkeys, but not of dogs, when given orally in a dosage of one or two tablets twice daily. Control experiments with enteric-coated placebos and potassium chloride indicate that it is the latter that is the responsible agent.

Boley *et al.* found that similar lesions could be produced in dogs sacrificed one to two weeks after suturing the tablets in position through an enterostomy. Their work also confirms that it is the potassium chloride that is responsible, and the incidence and severity of the lesions were related to the amount of potassium chloride.

An interesting feature of the lesion which does not seem to have aroused much comment is its narrow annular nature. Boley *et al.* found that the maximal histological changes in the dog intestine were in the submucosa, particularly the mural vessels, and are of the belief that ulceration of the mucosa is secondary to this. In our specimens no significant changes were noted in the blood-vessels.

Previous authors have stressed that, in view of the widespread use of enteric-coated diuretic and potassium chloride tablets, constricting ulcers of the small intestine must be a very rare complication. Morgenstern *et al.* record that after resection six of their patients resumed therapy without untoward effects. Two of our patients (Cases 2 and 3) have resumed therapy after operation. One (Case 2) has had attacks of abdominal pain which have been ascribed to his diverticulitis. In Case 3 recurrent pain was more clearly related to the tablets, and we doubt the wisdom of continuing treatment in such patients. Improvement followed cessation of the tablets in this patient, as in the case reported by Abbruzzese and Gooding.

In all previous reports that we have read the intestinal lesion has been resected. Two of our patients were treated by less radical measures, and we believe that this is justified if the condition is recognized in the poor-risk patient. It seems likely that with a knowledge of this syndrome a correct pre-operative diagnosis should be made, as in Case 6, and if the symptoms are recognized before the condition is established recovery may follow cessation of therapy. Though the lesions are few considering the quantity of enteric-coated preparations used, it may well be wise to avoid the enteric-coated preparation if potassium is required, and prescribe potassium separately in some other form.

### Summary

Six case reports are presented of small-bowel lesions associated with medication by an enteric-coated diuretic and potassium chloride tablet (Hydrosaluric-K). The lesions consist essentially of a localized stricture, usually associated with a circumferential ulcer. The lesion has been treated successfully by resection, entero-anastomosis, and enteroplasty. In one case perforation of the bowel had occurred; the other cases presented as intestinal obstruction. Improvement in recurrent symptoms after cessation of treatment was noted in one of the patients.

It appears that potassium chloride is the agent responsible.

<sup>1</sup> Esidrix-K is a preparation of diuretic with 1 g. of potassium chloride in an enteric-coated core, marketed in America by Ciba, and not to be confused with Esidrex-K, which is marketed by Ciba in this country and contains hydrochlorothiazide 12.5 mg. and potassium chloride 600 mg. in a slow-release wax matrix tablet.

Three of the patients were admitted under the care of Mr. Norman Gibbon. We wish to thank him for permission to record their case histories, and for his enthusiastic support throughout. We would also like to thank Mr. O. M. Jonathan for permission to record the case history of the patient (Case 4) admitted under his care.

ADDENDUM.—We have since seen a seventh case, which was admitted to hospital under the care of Mr. J. K. M. Rawlinson.

A stenosing circumferential ulcer of the small intestine was an incidental finding at operation for revision of colostomy and relief of subacute intestinal obstruction due to adhesions. Although stenosing, the ulcer was not obstructing. Non-specific ulceration was confirmed by biopsy and the stenosis relieved by enteroplasty.

The patient had had an abdomino-perineal resection of the rectum for carcinoma 15 years previously, and suffered from angina, for which he had been treated with Nephрил (poly-

thiazide with enteric-coated core of potassium chloride) for 2½ months followed by Centyl-K (bendrofluazide with potassium chloride) for six months prior to operation—both preparations one tablet three times a week.

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## Preliminary Communications

### Use of Trichlorethylene Inhalations during Physiotherapy

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Physiotherapists who treat thoracic surgical patients are well aware of the difficulty in obtaining the best results post-operatively because of pain, which so often limits the ability of the patient to carry out exercises. After surgery patients must breathe deeply, be able to carry out as full a range of arm movements as possible, and be able to cough sufficiently strongly to expectorate. These three functions are of great importance to recovery, and unless performed effectively from the first post-operative day difficulties can arise. Not only pain, but also fear of pain, can inhibit ventilatory efficiency. This can be gauged subjectively or measured by a reduction in vital capacity, peak flow, forced expiratory volume, PO<sub>2</sub>, or any other respiratory parameter; indeed, in many it may be obvious enough even in the most superficial clinical assessment.

Relief of pain is therefore of primary importance. The method most commonly employed is the administration of systemic analgesic drugs, but these cause respiratory depression and are not always completely effective in the face of active movement. Alternatively, nerve blocks with long-acting analgesic solutions or extradural blocks may be employed. Both can be effective; but long-acting solutions are notoriously unpredictable, while a continuous extradural block requires repeated "topping-up." Owing to the necessity for scrupulous asepsis, the latter technique is often time-consuming and may also lead to falls in blood-pressure, causing delay and wasting the time of the physiotherapist. Further, to give optimum results, both systemic analgesic injections and the "top-up" of an extradural block must be carefully timed. In practice, with overworked physiotherapists and inadequate nursing staff, particularly in the smaller centres, this is not always achieved. The more patients to be treated the greater are the difficulties, especially when it is realized that often, as in this hospital, each receives four treatments every day for the first three post-operative days.

The method described below has been designed to overcome these difficulties, at least in part, and to allow the physiotherapist to perform her work more efficiently without dependence on nursing or medical staff and hence with a considerable saving in time.

## METHOD

In effect, the post-operative patient is treated as a woman in labour, with the physiotherapist taking the place of the midwife. Analgesia is provided by the inhalation of 0.5% trichlorethylene delivered from an inhaler approved by the Central Midwives Board for use by midwives. The period of inhalation not only eases existing pain but also raises the pain threshold. Thus there is a feeling of relaxation and anxiety is removed. In consequence, patients are able to breathe more deeply, to move their arms more frequently, and to cough more vigorously. It was found that 8 to 12 breaths of 0.5% trichlorethylene were sufficient to give a beneficial effect for about two minutes. Often no more than six breaths were needed, but the amount required varied from patient to patient. Thus two to three periods of inhalations in the course of one physiotherapy treatment were usually needed. These inhalations were used in conjunction with, rather than as a substitute for, the normal post-operative injections of pethidine or papaveretum commonly given at intervals of four to six hours for the first 48 hours post-operatively. Such a combination—as in obstetrics—is ideal, but inhalations alone are also effective. Though inhalations can be repeated as often as they may be required, a cumulative effect sufficient to cause respiratory depression is not produced. A further advantage is the co-operation of the patient, which is maintained unless the inhalations follow heavy general sedation.

## RESULTS

During the past two and a half years 123 patients have been treated with trichlorethylene inhalations post-operatively: 91 were male and 32 female, with ages varying from the early 20s to the mid-70s.

The results are summarized in the Table. Most of the complete failures were encountered in the groups of patients undergoing lobectomy or pneumonectomy, but the total numbers do not warrant any particular significance being

Summary of Results

|                      | No. of Cases | Good     | Effect Moderate | Nil    |
|----------------------|--------------|----------|-----------------|--------|
| Lobectomy ..         | 35           | 19       | 13              | 3      |
| Pneumonectomy ..     | 17           | 5        | 9               | 3      |
| Pleurectomy ..       | 9            | 5        | 4               | 0      |
| Cardiac ..           | 15           | 10       | 5               | 0      |
| Other thoracotomy .. | 28           | 17       | 10              | 1      |
| Hiatus hernia ..     | 16           | 10       | 6               | 0      |
| Abdominal ..         | 3            | 1        | 2               | 0      |
|                      | 123          | 67 (54%) | 49 (40%)        | 7 (6%) |