REFERENCES

- Adlersberg, D., Schaefer, L., and Drachman, S. R. (1950). *J. Amer. med. Ass.*, **144**, 909.
- Bull, G. M., and Fraser, R. (1950). *Lancet*, **1**, 851.
- Carlisle, J. M. (1950). *British Medical Journal*, **2**, 590.
- Coburn, A. F. (1943). *Bull. Johns Hopk. Hosp.*, **73**, 435.
- Cochran, J. B., Watson, R. D., and Reid, J. (1950). *British Medical Journal*, **2**, 1411.
- Conn, J. W., Vogel, W. C., Louis, L. H., and Fajans, S. S. (1950). *J. Lab. clin. Med.*, **35**, 504.
- Dorfman, A., Bergenstal, D. M., Smull, K., Howard, R., Senz, E., Oleson, D., and Muller, R. (1951). *Proceedings of 2nd Clinical A.C.T.H. Conference*, **2**, 645. London.
- Reimers, E. J., and Ott, M. L. (1947). *Proc. Soc. exp. Biol., N.Y.*, **64**, 357.
- Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 545.
- Hetzl, B. S., and Hine, D. C. (1951). *Lancet*, **2**, 94.
- McEwen, C., Bunim, J. J., Baldwin, J. S., Kuttner, A. G., Appel, S. B., and Kaltman, A. J. (1950). *Bull. N.Y. Acad. Med.*, **26**, 212.
- Meade, B. W., and Smith, M. J. H. (1951). *Lancet*, **2**, 224.
- Perry, W. F. (1951). *Endocrinology*, **49**, 284.
- Proceedings of 2nd Clinical A.C.T.H. Conference* (1951). London.
- Reid, J. (1948). *Quart. J. Med.*, **17**, 139.
- Watson, R. D., and Sproull, D. H. (1950). *Ibid.*, **19**, 1.
- Roskam, J., Van Cauwenberge, H., and Mutsers, A. (1951). *Lancet*, **2**, 375.
- Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
- Smith, P. K., Gleason, H. L., Stoll, C. G., and Ogorzalek, S. (1946). *J. Pharmacol.*, **87**, 237.
- Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 199.
- Tarnoky, A. L., and Brews, V. Anne L. (1950). *J. clin. Path.*, **3**, 285.
- Van Cauwenberge, H., and Heugshem, C. (1951). *Lancet*, **1**, 771.
- Wilson, M. G., and Helper, H. N. (1951). *J. Amer. med. Ass.*, **145**, 133.
- Winter, C. A., Silber, R. H., and Stoerk, H. C. (1950). *Endocrinology*, **47**, 60.
- Wolfson, W. O., Beierwaltes, W. H., Robinson, W. D., Duff, I. F., Jones, J. R., Knorpp, C. T., Siemienski, J. S., and Eya, M. (1951). *Proceedings of 2nd Clinical A.C.T.H. Conference*, **2**, 95. London.

RELATION OF ELECTROLYTE CHANGES AND ADRENOCORTICAL ACTIVITY TO PARALYTIC ILEUS

BY

D. H. P. STREETEN,* D.Phil., M.B., M.R.C.P.
*Nuffield Demonstrator in Pharmacology, University of
Oxford*

AND

J. N. WARD-McQUAID, M.S., F.R.C.S.
*Graduate Assistant, Nuffield Department of Surgery,
University of Oxford*

(From the Radcliffe Infirmary, Oxford)

There has been much speculation about the cause of paralytic ileus ever since Thomas Sydenham (1666) differentiated the condition which he referred to as "true ileus" from the "bastard ileus" caused by mechanical obstruction. Sydenham thought that "true ileus" was due to fever which brought about a "commotion of the blood" so that "acid and malignant humours are lodged in the stomach and in those parts of the intestinal canal that lie nearest to it." Other "commotions of the blood" have continued to enjoy recognition as possible causes of the condition now known as paralytic ileus, and in recent years the suggestion has been made that electrolyte deficiencies may be among the responsible agents.

It has been known for some time that hypertonic sodium chloride infusions stimulate vigorous peristalsis in experimental animals (Hotz, 1909) and in patients with

paralytic ileus (Hughson and Scarff, 1924). More recently, French authors (Robineau, 1933; Lévy and Nora, 1935, 1946) have attributed paralytic ileus to the low concentration of chloride observed in the plasma and in the blood cells in this condition, and have attempted to prevent the onset of ileus by the routine administration of large amounts (45–50 g.) of sodium chloride daily in the immediate post-operative period. Marriott (1947) has also suggested that chloride deficiency may be the cause of some cases of ileus, and Streten (1950) has shown that the propulsive motility of actively contracting preparations of human intestine can be abolished by their immersion in fluid with a lowered chloride concentration similar to that which occurs in the plasma of patients with paralytic ileus.

Maddock (1939) found that post-operative hypochloræmia refractory to isotonic sodium chloride administration abated when the patients began to eat a normal diet. This observation prompted Ariel, Abels, Pack, and Rhoads (1943) to administer large amounts of protein orally and parenterally to patients with post-operative ileus associated with the same sodium-chloride-refractory hypochloræmia; their five patients all responded favourably. Randall, Habif, Lockwood, and Werner (1949) suggested that potassium deficiency was responsible for the syndrome described by Ariel *et al.* (1943), and hastened recovery by giving potassium solutions intravenously. Darrow (1950), too, stated that intestinal distension and paralytic ileus are among the results of potassium deficiency.

The clinical suggestion that potassium deficiency may cause paralytic ileus is considerably strengthened by a rapidly accumulating body of experimental evidence. Winter, Hoff, and Dso (1949) showed that the tone and motility of the whole gastro-intestinal tract were reduced, and the passage of a barium meal retarded, in rats made deficient of potassium either by repeated injections of deoxycortone or by lowering potassium intake. Webster, Henrikson, and Currie (1950) reported similar results in rats, but found that in dogs with potassium deficiency there was only a slight reduction in the strength and rate of rhythmical contractions of the alimentary tract. Streeten and Vaughan Williams (1952) have found that fluid transport by intestinal loops can be abolished in dogs by progressive sodium chloride depletion. The intestinal paralysis came on only when, as a result of chloride deficiency and adrenocortical stimulation, a rapid loss of cellular potassium took place, causing a sudden increase in the plasma concentration of this ion. When the propulsive motility of intestinal segments was abolished *in vitro* by reducing the sodium chloride content of the surrounding fluid, it was possible to demonstrate a large fall in the potassium concentration of the bowel wall and a consequent rise in the concentration of this ion in the surrounding fluid. In other unpublished experiments it was not possible to paralyse dog intestine by reducing the potassium concentration of the external medium to as low as 5 mg./100 ml. for periods of over an hour.

The recent evidence is therefore consistent with the view that intracellular, though not extracellular, potassium deficiency can cause paralysis of gastro-intestinal motility both *in vivo* and *in vitro*. The present study was undertaken in an attempt to discover the relation of potassium and chloride deficiency and adrenal cortical hyperactivity to the development of paralytic ileus in man.

*At present at Peter Bent Brigham Hospital, Boston, Mass., U.S.A.

Clinical Material and Methods

Thirteen patients with paralytic ileus were studied in Oxford, 11 during 1950 and 2 at the beginning of 1951 (Table I). Eosinophil and leucocyte counts were made

TABLE I.—Particulars of 13 Patients with Paralytic Ileus

Case No.	Sex	Age	Diagnosis and Operation	End of Ileus (Post-op Day)	Outcome
1	M	61	Acute obstruction due to carcinoma of pelvic colon: laparotomy and caecostomy	7th	Died 12th post-op. day
2	M	68	Perforation of sigmoid colon: laparotomy and coelostomy	8th	Recovery
3	M	66	Carcinoma of rectum: synchronous combined abdomino-perineal excision	6th	Died 9th post-op. day
4	M	48	Carcinoma of stomach: total gastrectomy, splenectomy, hemipancreatectomy	5th	Recovery
5	M	57	Perforated gastric ulcer with generalized peritonitis: operative repair	8th	"
6	M	44	Jejunal ulcer: high partial gastrectomy	6th	"
7	F	65	Carcinoma of head of pancreas: cholecyst-jejunostomy, jejuno-jejunostomy	5th	Recovery; died a month later
8	F	61	Appendicitis with general peritonitis: appendicectomy	8th	Recovery
9	M	21	Appendicitis: appendicectomy. General peritonitis: pelvic abscess	10th	"
10	M	37	Acute pancreatitis: laparotomy. Burst abdomen 10th post-op. day	7th	"
11	F	49	Ruptured tubo-ovarian abscess: salpingo-oophorectomy	7th	"
12	M	44	Duodeno-jejunal obstruction due to metastases of carcinoma of kidney: gastro-enterostomy. Burst abdomen 9th post-op. day	8th	Recovery; died 11 days later from sudden haemorrhage
13	F	43	Mesenteric thrombosis: resection 6 feet of ileum	6th	Recovery

by Randolph's (1944) method, and packed cell volumes with matched Wintrobe tubes spun at 3,000 r.p.m. for 30 minutes. Trichloroacetic acid extracts of blood cells were prepared for estimations of mean erythrocyte potassium concentration (M.E.K.C.) with a flame photometer, which was also used for estimations of potassium and sodium in plasma and in 24-hour collections of urine, gastro-intestinal aspirations, and H_2SO_4 -extracts of faeces (Peters and Van Slyke, 1932). Chloride concentrations in plasma, whole blood, urine, aspirations, and faecal extracts were estimated by Van Slyke and Hiller's (1947) modification of the micro-method of Sendroy (1937). Mean corpuscular chloride concentrations (M.C.Cl.C.) were calculated from the formula

$$M.C.Cl.C. = \frac{\text{whole blood Cl} - \left(\frac{\text{plasma Cl} \times 100 - \text{haematocrit}}{100} \right)}{\text{haematocrit}} \times 100$$

For this estimation the haematocrit was read to the top of the buffy coat (layer of leucocytes), since preliminary studies showed that leucocytes and erythrocytes had approximately similar chloride concentrations. After recovery, patients were given a diet of known electrolyte content.

Repeated references will be made in this paper to unpublished results of blood chemical and balance studies made on a series of seven patients for four to six days before and six to ten days after a variety of elective major surgical procedures comparable to the operations which had preceded the onset of ileus in the present series of patients.

Onset and End of Ileus.—The onset and end of paralytic ileus cannot be defined accurately. In these patients the diagnosis rested on the absence of bowel sounds on repeated examination, failure to pass flatus or faeces, and vomiting or the aspiration of large volumes of fluid by an indwelling naso-gastric tube, associated with abdominal distension, after the third post-operative day. The ileus was thought to be over when the bowels were opened or flatus was passed repeatedly, although the distension often persisted.

Management of Cases

All the patients received penicillin, and all but one had soluble sulphadimidine injections. Streptomycin was also given to eight patients who were thought to have peritonitis. Injections of morphine were given occasionally to most of the patients, but more frequently to only three of them. Amidone replaced morphine in some of the later patients. Naso-gastric suction by Ryle's tube was used in 11 patients, and in only two was a Miller-Abbott tube passed. Most of the patients were allowed 1 oz. (30 ml.) of fluid by mouth hourly, and were given combinations of water, Ringer's solution, 5% dextrose, fruit juice, citrated milk, and 1% potassium chloride in orange juice. Three blood transfusions (1 or 2 pints—570 or 1,140 ml.—each) were given to six patients, three of whom also received plasma infusions. The first six patients received saline, dextrose, and Ringer's solution intravenously, while the other group of seven patients was given in addition infusions of Darrow's solution (NaCl 6 g., KCl 2.7 g./litre) in an attempt to correct the deficiency and replace the daily losses of potassium. Two of the first group of patients, Cases 1 and 3, died six and three days respectively after having repeated bowel movements. All seven patients in the second group recovered, one (Case 7) dying a month later from generalized carcinomatosis, and another (Case 12) dying from sudden gastro-intestinal haemorrhage 11 days after recovery from ileus, while he was up and about taking a normal diet.

Changes in the Eosinophil and Leucocyte Counts

When the patients were first seen the eosinophil count was below 60 per c.mm. in 9 of 11 cases examined. Serial eosinophil counts were made in seven patients who survived (Fig. 1) and two who died. The count remained low for as long as the ileus continued, but rose abruptly on the day

FIG. 1.—Eosinophil counts in seven patients with ileus who survived. The vertical line indicates the end of ileus, and the ciphers are the patients' serial numbers (see Table I).

the ileus was considered to have ended, or immediately before or after this day. Thereafter the count fluctuated within normal limits. The two fatal cases had normal eosinophil counts when they were first seen four and five days after operation. After a few days both patients passed large amounts of intestinal contents through a caecostomy and colostomy respectively, and this continued, while the leucocyte and eosinophil counts fell progressively, until the patients died.

A leucocyte count of less than 4,000 per c.mm. was observed at some stage of the ileus in 6 of the 13 cases, including two of the five patients with very severe drum-like distension. Most of the leucocyte counts were within normal limits (4,000–10,000 c.mm.), however, in spite of the fact that many of the patients had severe infections. These findings confirm the report of Van Duyn (1942) that leucopenia often occurs in patients with severe abdominal distension.

Blood Electrolyte Changes

Potassium.—The plasma potassium concentration varied widely in the 10 patients in whom repeated estimations were made, and no consistent changes were observed. Low

FIG. 2.—Mean erythrocyte K concentrations in six patients with paralytic ileus. The vertical line indicates the end of ileus

values varying from 9.4 to 15.2 mg./100 ml. were recorded in five patients when first seen. At the time of recovery two of these patients showed a rise which continued, but four still had low values (10.3 to 14.5 mg./100 ml.) several days later. The M.E.K.C. in most of the cases of ileus was not below the levels (359–418 mg./100 ml., mean 382.2, S.D. 23.5) observed on the fourth post-operative day in normal convalescence. At the time of recovery from ileus, however, five out of six patients showed an increase, but

one a progressive fall in M.E.K.C. (Fig. 2). In two of three other patients in whom only single estimations were made, low values (311 mg./100 ml. and 314 mg./100 ml.) were found several days after recovery. No consistent changes could be found in the ratio between the erythrocyte and plasma potassium concentrations.

Chloride.—The plasma concentration of chloride was below 560 mg./100 ml. (as NaCl) in all of the patients when first seen in ileus (Table II). In 9 of the 13 patients there was a gradual rise in plasma chloride concentration from when they were first seen, followed by a more rapid rise to normal levels (550–630 mg./100 ml.) on the day of recovery, or immediately before or after that day. In two other cases the values remained low for several days after the recovery of bowel function. In patients on whom elective surgical operations were performed the mean of the estimations of M.C.Cl.C. has been found to be 318 mg./100 ml. (S.D. 22.6) before the operations and 313 mg./100 ml. (S.D. 21.9) on the fourth post-operative day; all the estimations done four days after operation fell between 280 and 333 mg./100 ml. Seven out of 10 of the present series of patients had an M.C.Cl.C. below 280 mg./100 ml., and one patient had a low normal value at 286 mg./100 ml. Normal levels were reached in all patients after recovery from ileus, though this usually took a few days. In three of the patients there was a greater reduction in mean corpuscular than in plasma concentration. This was reflected in a cell/plasma ratio which was below the normal range (0.47 to 0.59, mean 0.54, S.D. 0.037) found in surgical patients before operation. Normal cell/plasma chloride ratios were reached on recovery in these patients.

Sodium.—The plasma sodium concentration was reduced below 315 mg./100 ml. in 5 of the 40 patients in whom it was estimated in ileus. In only one of these patients did the concentration rise above 315 mg./100 ml. on the day of recovery or during the succeeding two days, normal levels being reached in the remainder from three to five days after bowel movements had returned.

Changes in the Electrocardiogram

Electrocardiograms were obtained on five patients during ileus, and each showed evidence of potassium deficiency, with depression of the ST segment and prolongation of the Q-T interval.

Since the Q-T interval varies with the heart rate, the observed duration of the Q-T interval was compared in each patient with the normal duration, calculated from the formula (Bazett, 1918–20) $Q-T = K \times \sqrt{\frac{60}{\text{heart rate}}}$,

where $K=0.40$ for women and 0.37 for men. The observed Q-T intervals were in all cases longer than the normals calculated from the formula; after recovery from ileus there was a tendency to return towards the normal Q-T duration in the two patients examined.

TABLE II.—Results of Plasma Chloride Estimations in 13 Patients with Paralytic Ileus (Values in mg./100 ml., as NaCl)

Case No.	Days Before Recovery					Day of Recovery	Days After Recovery								
		-4	-3	-2	-1		+1	+2	+3	+4	+5	+6	+7	+8	
1				495	527	559	564	538	529	572	703	Death			
2		525			562	574	567	562							
3				533	504	506	590	707	699	Death					
4				505	540		595		580					575	
5		522	534	526	523		554	558			549				
6			551			550			549	568					
7		445	406		506	480			497	477				518	615
8		496									579				
9		534			540	548	585	574	565		564			523	
10	545				524	565		574		529					
11							542								
12		454	522	484		479	493				579	554			
13			559		530	550		580				600			11th 665
Mean ..		508.0			528.4	534.6	561.3	584.7	563.6	572.8					

Gastro-intestinal Aspirations

Large amounts of sodium, chloride, and potassium were lost in the aspirated gastro-intestinal contents (Table III). The concentrations of the electrolytes varied somewhat

TABLE III.—*Electrolytes in Gastro-intestinal Aspirations*

	Mean	Range
Na ..	200 mg./100 ml.	150–343 mg./100 ml.
Cl (as Cl) ..	303 mg./100 ml.	178–426 mg./100 ml.
K ..	37 mg./100 ml.	22–89 mg./100 ml.

among the patients in the series, but were surprisingly constant from day to day in any one of the five patients who received Ringer's solution, citrated milk, or water in hourly volumes of 1 oz. (30 ml.) by mouth. Three of the patients were given concentrated potassium chloride solutions by mouth during ileus, but it was found that a variable proportion, frequently almost all, of the ingested potassium was recovered in the gastric aspirations, indicating that little reliance could be placed on absorption of potassium administered by this route in paralytic ileus.

A striking change was observed in the colour of the 24-hour specimens of aspirated material. When the patients were first seen the aspirations were dark green and contained much biliverdin, but little or no bilirubin. A day or two before the end of ileus the aspirated material became yellow or reddish, and always contained bilirubin (positive van den Bergh reaction) but no biliverdin.

Urine and Faeces

The urine passed during the 24 hours after the patients were first seen with ileus was always small in volume; it contained very low concentrations of sodium and chloride and a high concentration of potassium.

FIG. 3.—Water, Cl, Na, and K balances in Cases 5 and 6. Daily intake is charted from the base-line upwards, and daily output from the top of each intake column downwards. Urinary output is unshaded and separated from aspirations by a dotted line; balances are cross-hatched. Balances above the base-lines are therefore positive. No allowance has been made for insensible water loss. The end of ileus is indicated by the arrows.

After treatment for a variable number of days there was a sudden reduction in the urinary potassium and an increase in urinary sodium and chloride excretion, all of which occurred on the day of recovery from ileus, or one to two days before or after this day. The increase in sodium excretion preceded that of chloride in most patients. The reduced potassium and increased sodium and chloride output at the time of recovery occurred in spite of the fact that the intake of these ions was kept fairly constant or was changed in the directions opposite to the urinary changes. Fig. 3 shows that these urinary changes occurred at about

the same time as the rise to normal levels of the eosinophil count in the seven patients (Cases 7 to 13) in whom both estimations were made.

The sodium, chloride, and potassium content of the faeces was estimated in five patients (Cases 8, 9, 10, 12, and 13). Some of the patients in the series passed repeated large diarrhoeal stools and suffered from incontinence on their recovery from ileus, and a complete collection of faeces was impossible. In any one of the patients the faecal electrolyte concentrations were fairly constant, daily variations from the mean being seldom more than 30%. The variation between patients was very large indeed, sodium concentration varying between 41 and 630, chloride (as Cl ion) between 52 and 231, and potassium between 66 and 542 mg./100 ml.

Balances

The water, chloride, sodium, and potassium balances in Cases 5 and 6 are shown in Fig. 3. As in Cases 7 to 13 (see Fig. 4), there was a sudden reduction in the large urinary output of potassium at about the time of recovery from ileus.

A marked diuresis of sodium, chloride, and water took place at the time of recovery in both patients. It is evident that these changes in electrolyte excretion were in the opposite direction to the variations in their intake and could not be attributed to this cause. Both patients retained large amounts of water, sodium, and chloride during ileus, but were restored to normal balance within two to three days of the return of bowel function. Delay in the excretion of administered sodium chloride may have been partly responsible for the sudden diuresis of sodium and chloride at the time of recovery. However, excretion of a sodium chloride load in normal individuals is seldom as long delayed as in these patients, in whom the occurrence of a sudden rise in the eosinophil count at the same time provided additional evidence of a hormonal mechanism inducing the changes in urinary electrolyte excretions.

The balances in the patients in whom faecal losses were estimated indicated that the apparent positive balances of sodium and chloride during ileus and of potassium after recovery cannot be explained as being due to the loss of these electrolytes into the bowel lumen. The negative potassium balance present in ileus was replaced after recovery by a period of great potassium retention; the mean daily retention of potassium, in patients in whom faecal losses were estimated, was 2.5 g. for the first two to four days after recovery.

Discussion**Adrenocortical Activity in Ileus**

An eosinopenia was observed in 9 of 11 patients with paralytic ileus. At this time, more than three days after operation, the eosinophil count would be expected to be within normal limits if recovery was uncomplicated (Roche, Thorn, and Hills, 1950; Coppinger and Goldner, 1950; Johnson, Conn, Iob, and Collier, 1950). On the other hand, in patients who develop infection or other post-operative complications causing prolongation of the usual adreno-

FIG. 4.—Mean eosinophil count and daily urinary output of K and Cl in seven patients (Cases 7 to 13). The end of ileus is indicated by a vertical line.

cortical response to the operation, eosinopenia will persist, often in the absence of leucocytosis, as long as the complication is present, in the same way as eosinopenia will be observed for the full duration of continuous intravenous A.C.T.H. infusions lasting as long as 10 days (Thorn, 1952). The persistent eosinopenia in paralytic ileus even in the presence of normal or lowered leucocyte counts probably, therefore, indicates an unusual prolongation of the normal post-operative increase in the secretion of 11-oxysteroids by the adrenal cortex. It is well known that these steroids promote an increase in the urinary excretion of potassium, and all of our patients were found to have a high output of potassium in at least the first of the 24-hour specimens of urine analysed four or more days after operation. Wilkinson, Billing, Nagy, and Stewart (1950b) and our own unpublished results have shown that at this stage in a normal convalescence the urinary potassium output has fallen after its initial post-operative increase. The presence of persistent adrenocortical hyperactivity in ileus is further indicated by the sudden reduction in urinary potassium output and the diuresis of water, sodium, and chloride which occurred at the end of ileus.

Potassium Deficiency

After a prolonged urinary excretion of potassium and in the absence of its replacement, these patients with ileus would be expected to be severely deficient in potassium. The loss of large amounts of gastro-intestinal contents still further aggravated this depletion. It is difficult to demonstrate cellular deficiency of potassium which may be associated with a normal or raised plasma potassium concentration. If the loss of potassium from the cells continues for long enough, urinary excretion of the ion will eventually result in a lowered plasma potassium level, as was found in 5 out of 10 of our patients. A deficiency of cellular potassium is strongly suggested by the findings in the five patients on whom electrocardiograms were done. The results of the M.E.K.C. estimations failed to provide further definite evidence of cellular potassium deficiency. However, there was a sharp rise in M.E.K.C. at the time of recovery from ileus in five of the six patients in whom repeated estimations were made. This rise occurred at about the same time as the increase in the eosinophil count and was reminiscent of a similar rise in M.E.K.C. which coincided with the end of the eosinopenia between two and three days after uncomplicated operations. Strong evidence of potassium deficiency during ileus was obtained from the balance studies, which demonstrated that large quantities of potassium were retained after recovery in all cases.

Chloride Changes

The changes in chloride were probably of less consequence. All the patients had a lowered plasma chloride concentration, usually associated with a relatively slight reduction in plasma sodium. The lowered plasma chloride concentration cannot, however, be attributed to urinary excretion of chloride, since there is retention of both chloride and sodium with the loss of only very small quantities of both these ions in the urine for periods of four to eight days after major operations. Furthermore, our patients with ileus all had very low urinary chloride concentrations when first seen. The reduced plasma chloride is possibly secondary to loss into the alimentary tract, or it may be the unexplained accompaniment of cellular potassium deficiency, to which Darrow (1948) and others have drawn attention. The reduced erythrocyte chloride concentration in ileus was also found by the French workers Robineau (1933) and Lévy and Nora (1933), but it is impossible to say whether this reduction is attributable to potassium depletion, or how far chloride deficiency *per se* contributes to the paralysis of the bowel in ileus.

Pathogenesis of Ileus

In patients with paralytic ileus there is good evidence both of prolonged adrenocortical hyperactivity and of the potassium deficiency which this is known to produce.

Experimental work has shown that deficiency of intracellular potassium results in a condition in animals indistinguishable from paralytic ileus in man. It seems reasonable, therefore, to suggest that the gastro-intestinal features of ileus may be due to potassium depletion, which, in turn, may result from prolonged adrenocortical hyperactivity and reduced intake of potassium. Three objections to this hypothesis immediately come to mind.

First, cortisone and A.C.T.H. have often been given in high doses without potassium salts, and, while alkalosis with low plasma chloride and potassium concentrations has resulted, there have been no reports of ileus. It is possible that the loss of potassium is more severe or more rapidly produced in patients developing ileus than in those receiving hormonal treatment; for Winter *et al.* (1949) have shown that deoxycortone, which is more potent in its potassium-diuretic effects than is cortisone, impairs the gastro-intestinal motility of rats. This possibility is strengthened by the fact that patients on cortisone or A.C.T.H. therapy are usually eating a normal diet, with a fairly high potassium content, whereas in patients developing ileus there has almost always been a period of at least three days after operation during which virtually no potassium has been taken. Evidence from three of our patients suggests that paralytic ileus is caused not by adrenocortical hyperactivity *per se* but by the potassium deficiency which it induces. In Case 9 paralytic ileus ended when the potassium deficiency had been overcome, but the eosinopenia persisted because of adrenocortical activity induced by a large pelvic abscess. On the other hand, the two fatal cases had normal eosinophil counts when first seen. Both patients were, however, severely depleted of potassium because of the unreplaced losses of this ion during the immediate post-operative period.

A second objection, which is more difficult to reconcile with the hypothesis advanced, is that many patients will recover from paralytic ileus without receiving potassium salts and without complete recovery from electrocardiographic and other signs of potassium deficiency. It may be that the abrupt termination of adrenocortical hyperactivity found at the end of ileus causes a redistribution of body potassium, resulting in a replenishment, from skeletal muscle stores, of the potassium contained not only in the erythrocytes, as has been shown, but also in the intestinal muscle.

Thirdly, while the increased adrenocortical activity during ileus and its abrupt termination at the end of ileus suggests an intimate relationship between adrenocortical hyperfunction and paralytic ileus, it may be argued that ileus is the cause, and not the result, of the increased adrenocortical secretion. This possibility cannot be eliminated, but seems unlikely. Most types of "stress" will certainly stimulate an increase in the output of steroids by the adrenal cortex. It is possible that intestinal paralysis *per se* may have the same effect, but there is no direct evidence that it does.

In conclusion, there would seem to be more reason to believe that infection (which was present in eight cases in this series), or some other agent, is responsible for the excessive adrenocortical activity which, through potassium deficiency, may be a factor in causing ileus.

Intravenous Therapy in Paralytic Ileus

A full discussion of the treatment of ileus is beyond the scope of this paper. Whether deficiency of potassium is or is not the cause of post-operative paralytic ileus, patients with this condition are almost always deficient in potassium, and will sometimes die unless this deficiency is corrected. If the depletion of potassium, and the losses of sodium and chloride in the aspirations can be corrected, and complications treated, most patients will survive until increased adrenocortical activity subsides and ileus ends.

Intravenous therapy aimed at replacing daily losses and rectifying existing deficiencies is governed by the normal rules (Darrow and Pratt, 1950). The Fantus test (1936) is a convenient means of estimating losses of chloride in the aspirated gastro-intestinal fluids, though its use as an indication of chloride deficiency in the urine is fallacious in the

presence of adrenocortical hyperactivity. If facilities for determining daily potassium losses are not available, the figures obtained in this study afford a rough guide to the patients' requirements. Thus, 1.5-3 g. of potassium was lost each day in the urine, about 0.4 g. of potassium per litre in the aspirations, and an unknown amount into the distended bowel, the fluid faeces after recovery containing 0.5 to 5 g. of potassium per litre. It is convenient to replace the losses of sodium, chloride, and potassium in the aspirations by administering 250 ml. of Darrow's solution (NaCl 6 g. and KCl 2.7 g. per litre) for each litre aspirated. More concentrated potassium chloride solutions, containing no sodium, such as that of Davidsen and Kjerulf-Jensen (1951) (KCl 3.8 g. and dextrose 34 g. per litre), are indicated for the correction of the initial potassium deficiency, but the solutions must be given slowly and only in the presence of adequate urine output, sodium chloride or dextrose solutions being given first, if necessary.

Ramasarma (1951) states that clinical benefits result from the administration of amino-acid solutions to surgical patients, but Wilkinson *et al.* (1950a) consider that intravenous protein is not retained in the post-operative "katabolic" phase.

Suction and the Relief of Distension

In most of our patients symptomatic relief was obtained by Ryle's tube, but patients with severe distension can be afforded greater relief by long intestinal tubes (Miller and Abbott, 1934; Cantor, 1946; Harris, 1945). The importance of distension as the major factor in paralyzing the bowel has probably been over-estimated, as eight of our patients remained distended for some days after the return of intestinal movements. In any event, intestinal tubes afford great symptomatic relief and probably reduce the incidence of chest complications, and organic obstruction due to kinking of the bowel.

A large oral intake of fluid before normal intestinal motility is restored appears to encourage paralysis (Begg, 1943).

Stimulation of the Bowel

Attempts to stimulate intestinal motility by such drugs as posterior pituitary extract, neostigmine, and diisopropyl fluorophosphate are of little value, certainly until electrolyte deficiencies have been corrected (Streeten, 1950), and may even be harmful (Devine, 1946).

Sedation

Patients with ileus are often justifiably worried and usually badly in need of sleep. Morphine has been shown to cause tonic contraction of the intestine and abolition of propulsive movements for long periods in dogs: it therefore cannot be said to "rest" the bowel. It may be beneficial to begin treatment with a single injection of morphine which may reduce distension, but repeated injections would seem likely to prevent the return of normal intestinal propulsion. Amidone in therapeutic doses has, however, little effect on motility (Vaughan Williams and Streeten, 1950, 1951). Our impression from a clinical trial in which morphine and amidone (10 mg.) were given to 30 alternate patients after similar major operations was that the analgesic effects of the drugs were similar, while the patients who received the amidone were more co-operative and suffered less from nausea.

Summary

Thirteen patients with paralytic ileus were studied in an attempt to discover the relation of adrenocortical hyperactivity and of potassium and chloride deficiency to the development of this condition.

There was evidence of adrenocortical hyperactivity during ileus, with abnormal prolongation of the post-operative eosinopenia, excessive potassium loss in the urine, and retention of water, sodium, and chloride.

On recovery the eosinophil count rose, and there was a diuresis of water, sodium, and chloride and a retention of potassium.

Evidence of potassium deficiency rested on excessive loss during ileus and retention after recovery: it was confirmed by electrocardiographic changes. In five out of ten patients the plasma potassium was low and, although the mean erythrocyte potassium concentration was not below normal levels in ileus, there was a definite increase in five out of six patients on recovery.

Low plasma and blood-cell chloride concentrations were found in nearly all patients with ileus. Normal values were regained at about the time of recovery.

There is strong experimental evidence that potassium deficiency produces a state akin to ileus in rats and dogs. The hypothesis that the gastro-intestinal features of paralytic ileus in man are due to potassium depletion as the result of adrenocortical hyperactivity is considered, and the difficulties in accepting this view are discussed.

The importance of replacing lost electrolytes, particularly potassium, in ileus, is emphasized. Amidone is probably superior to morphine as an analgesic in ileus. Most patients recover provided their electrolyte balance is restored and the complications are dealt with.

We are indebted to Mr. D. A. Abernethy for allowing us to treat eight of these patients, and to other surgeons of the Radcliffe Infirmary for allowing us to investigate, and in some cases to treat, the remainder. Our thanks are due to Dr. L. Leyton, of the Department of Forestry, University of Oxford, for the use of his flame photometer; to Miss McLarty for the diagrams; to the dietitians, Miss Hemmin and Mrs. Westland; and to the ward sisters, particularly Sister Whitcombe.

REFERENCES

- Ariel, I., Abels, J. C., Pack, G. T., and Rhoads, C. P. (1943). *J. Amer. med. Ass.*, 123, 28.
 Baxter, H., Schiller, C., Whiteside, J., and Stralith, R. E. (1951). *Plast. reconstr. Surg.*, 7, 24.
 Bazett, H. C. (1918-20). *Heart*, 7, 353.
 Begg, R. Campbell (1943). *S. Afr. med. J.*, 17, 26.
 Cantor, M. O. (1946). *Amer. J. Surg.*, 72, 137.
 Coppinger, W. R., and Goldner, M. G. (1950). *Surgery*, 28, 75.
 Darrow, D. C. (1948). *Bull. N.Y. Acad. Med.*, 24, 147.
 — (1950). *New Engl. J. Med.*, 242, 978.
 — and Pratt, E. L. (1950). *J. Amer. med. Ass.*, 143, 365, 432.
 Davidsen, H. G., and Kjerulf-Jensen, K. (1951). *Lancet*, 2, 17.
 Devine, J. (1946). *Erit. J. Surg.*, 34, 158.
 Fantus, B. (1946). *J. Amer. med. Ass.*, 107, 14.
 Harris, F. I. (1945). *Surg. Gynec. Obstet.*, 81, 671.
 Hotz, G. (1909). *Mitt. Grenzgeb. Med. Chir.*, 20, 257.
 Hughson, W., and Scarff, J. E. (1924). *Bull. Johns Hopk. Hosp.*, 35, 197.
 Johnson, H. T., Conn, J. W., Iob, V., and Collier, F. A. (1950). *Trans. Amer. surg. Ass.*, 68, 54.
 Lévy, M., and Nora, G. (1935). *Arch. Mal. Appar. dig.*, 25, 190.
 — (1946). *Ibid.*, 35, 67.
 Maddock, W. G. (1939). *Amer. J. Surg.*, 46, 426.
 Marriott, H. L. (1947). *British Medical Journal*, 1, 285.
 Miller, T. G., and Abbott, W. O. (1934). *Ann. intern. Med.*, 8, 85.
 Peters, J. P., and Van Slyke, D. D. (1932). *Quantitative Clinical Chemistry*. Baillière, Tindall & Cox, London.
 Ramasarma, G. B. (1951). *Int. Abstr. Surg.*, 93, 105.
 Randall, H. T., Habif, D. V., Lockwood, J. S., and Werner, S. C. (1949). *Surgery*, 26, 341.
 Randolph, T. G. (1944). *Amer. J. clin. Path.*, 14, Tech. Suppt. 48.
 Robineau, M. (1933). *Bull. Soc. Nat. Chir.*, 59, 519.
 Roche, M., Thorn, G. W., and Hills, A. G. (1950). *New Engl. J. Med.*, 242, 307.
 Sendroy, J. (1937). *J. biol. Chem.*, 120, 335, 405.
 Streeten, D. H. P. (1950). *Surg. Gynec. Obstet.*, 91, 421.
 — and Vaughan Williams, E. M. (1952). *J. Physiol.* In press.
 Sydenham, T. (1666). *The Works of Thomas Sydenham*, translated by R. G. Latham. The Sydenham Society, London, 1848.
 Thorn, G. W. (1952). Personal communication.
 Van Duyn, J. (1942). *Arch. Surg., Chicago*, 44, 339.
 Van Slyke, D. D., and Hiller, A. (1947). *J. biol. Chem.*, 167, 107.
 Vaughan Williams, E. M., and Streeten, D. H. P. (1950). *Brit. J. Pharmacol.*, 5, 584.
 — (1951). *Ibid.*, 6, 263.
 Webster, D. R., Henrikson, H. W., and Currie, D. J. (1950). *Trans. Amer. surg. Ass.*, 68, 458.
 Wilkinson, A. W., Billing, B. H., Nagy, G., and Stewart, C. P. (1950a). *Lancet*, 1, 533.
 — (1950b). *Ibid.*, 2, 135.
 Winter, H. A., Hoff, H. E., and Dso, L. (1949). *Fed. Proc.*, 8, 169.