Second Opinion, Please

A Gastrointestinal Problem

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205, Shard End Crescent, Birmingham, 34

Dear John,

I need your help once more with a gastrointestinal problem which I feel is a bit different from the usual ones that I refer to you, mainly because the history is rather vague and doesn't fit into any particular pattern. All the same I feel there may be an organic basis for the symptoms.

This man, Mr. K. L., is 63 years-old, and has been my patient for the past ten years. I saw very little of him until two years ago, when he had a small stroke consisting of a partial left hemiplegia, from which he made a full recovery in a few days. He was found to be consistently hypertensive (B.P. 180/115) and has been treated on a mild hypotensive drug, Salupres, since then.

Immediately following the stroke he was constipated, but two weeks later, when mobile, he tended to get occasional bouts of diarrhoea, which have occurred on three or four occasions since then consisting of one or two loose motions without blood or mucus. He had had domestic problems since the time of the stroke and at first I tended to regard the diarrhoea as functional. In the past week or two he has had some non-colicky central abdominal pain, recurring roughly one hour after meals, but never really assuming a consistent pattern either in location or timing. There is no weight loss and his appetite is good. He doesn't look ill and I would hope that there is nothing sinister underlying this, but feel that further investigation is indicated.

General Hospital, Birmingham

Dear Brian,

I see what you mean, this is rather an unusual story. Part of the problem is the great difficulty in obtaining a coherent history; I suspect that some of this may be due to the effects of his probable cerebral ischaemia. The complaints relate to the alimentary tract and appear to be principally poorly localized abdominal pain and a bowel habit that is looser and more frequent than before his stroke. There seems to be some time relationship between the pain and the taking of food but nothing he has tried seems to relieve the pain.

A thorough physical examination, including a sigmoidoscopy limited to 15 cm by a loaded colon, failed to reveal any abnormal physical signs and his haemoglobin was 14·6 g.

It is tempting to dismiss these symptoms as "functional" but like you I have a sneaking suspicion that something is amiss. In addition to the haemoglobin I asked for the E.S.R. to be measured and this was 25 mm. While I would not attach too much weight to this finding it confirms our belief that we must investigate this man's gastrointestinal tract.

It is difficult to know where to start; the type of pain and the altered bowel habit suggests that he might have diverticular disease or the irritable colon syndrome, but the presence of a stool-packed sigmoid is rather against this. As there does seem to be some relationship to eating I will begin with a barium meal and take a 24-hour film to gain some extra information about the large bowel as a bonus. As we have facilities for a multi-channel biochemical "profile" on his serum this will act as a useful screening test.

I will write to you again as soon as we have completed the preliminary investigations.

General Hospital, Birmingham

Dear Brian,

Following my telephone call after the first round of investigations, I now write to report the results of our rather extensive, but still inconclusive, outpatient studies. First let me justify our persistence with investigations after my initial remarks suggesting that the complaints may be functional. His symptoms persist, his serum albumin has been low on two occasions (3·1 and 2·9 g/100 ml), and his E.S.R. is now 62 mm. He has lost only one kilogramme in weight, but I feel sure that there must be some organic disease.

When the barium meal, chest *x*-ray, the rest of the liver-function tests, and the serum electrolytes and calcium showed no abnormality we continued with a barium enema, half expecting to find a colonic carcinoma. There was no abnormality, not even anything we could label "irritable colon." We than began to suspect the possibility of some occult intra-abdominal carcinoma (particularly as he began to complain of the loose stools being particularly offensive) or the possibility of a pancreatic neoplasm, and felt that at least it would be worth looking for some confirmatory signs. He has now had a three day faecal fat analysis, a hypotonic duodenogram, a cholecystogram, and a scintillation scan of the liver and pancreatic areas; all completely normal though the pancreatic scan gave a rather poor outline of the pancreas. These rather expensive investigations are poor methods of searching for a pancreatic neoplasm, but at least they are safe and do not necessitate inpatient investigation.

Despite the absence of supporting signs, the possibility of chronic gut ischaemia must still remain and we have considered the possibility of selective coeliac and mesenteric arteriography. With our present facilities and experience, the risks of these investigations are still a deterrent and for the present we will keep them in reserve.

I am sure you must be saying to yourself, "if you are so suspicious that there is some mischief in the abdomen, why not perform a laparotomy and see what is going on?". I

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acknowledge this criticism and have asked the same question. However, there is no evidence that early diagnosis of a pancreatic carcinoma improves the prognosis and with his past history of thrombotic episodes I would prefer to postpone laparotomy and keep him under regular review. Fortunately, he finds now that the attacks of pain are less severe and seems to need no symptomatic treatment. As you have such a well organized review system in your practice it will be most convenient for him to report to you once a week. Please refer him back to me as soon as you think it indicated.

205, Shard End Crescent, Birmingham, 34

Dear John,

I am sorry to bother you again, but I am afraid that our mutual friend is still in trouble. He remained reasonably well for some weeks after your investigations, but now has further intermittent abdominal pain of the same vague nature as before. In spite of the previous negative findings, I feel that you ought to see him once more. (Incidentally, his blood pressure has remained normal since I stopped his therapy some weeks ago.)

205, Shard End Crescent, Birmingham, 34

Dear John,

Since sending you my last letter I am afraid that the picture has changed during the last few days and I would like you to see Mr. K.L. urgently. His pain is more severe and he has started to vomit. He has ankle oedema and albuminurea. There has been a considerable weight loss and I feel that he must have a carcinoma somewhere in the gastrointestinal tract.

General Hospital, Birmingham

Dear Brian,

I am sure that you were fascinated to receive the copy of the operation note on this man last week. Our suspicion on macroscopic grounds—that these were simple strictures due to potassium tablet ulceration—has now been confirmed by Professor D. B. Brewer.

Mr. K.L. came up to the clinic on the day you wrote your last letter and we admitted him directly to the ward. He was obviously very much worse than when he last attended. Though the vomiting stopped, he was dehydrated with a non-tender resonant distended abdomen, obstructive type of bowel sounds, and ankle oedema. After rehydration his haemoglobin was only 10·9 g and his albumin was 2·2 g. An erect plain *x*-ray of the abdomen showed small bowel fluid levels but there was gas in the large bowel indicating that the obstruction was incomplete. While waiting to bring him to an optimum state with intravenous blood and electrolytes we had some barium run through the gut from above and the site of the obstruction was localized to the ileum but its nature was not demonstrated.

As you will have read, we found multiple strictures of the ileum. The appearances were unlike Crohn's disease and the diagnosis began to dawn on us (about time too!). When the resected 20 cm of gut was cut open it showed three tightly encircling scarred ulcers. Two lesser areas of narrowing were then detected higher in the small gut 140 cm from the beginning of the jejunum, but they were not causing obstruction and were left.

He has made an excellent recovery without any complication and left hospital today.

205, Shard End Crescent, Birmingham, 34

Dear John,

I am very relieved to know that Mr. K.L. has made a good recovery following the resection of the affected ileum.

You will be interested to know that I had another patient, a year ago, with the same complications from Salupres therapy. He was a man about 56 years-old who had been on the drug for two years, but suddenly developed signs of small bowel obstruction. At operation there was a stricture of the ileum four feet from the ileocaecal valve. The resected section showed evidence of ulceration consistent with potassium therapy.

I have reported both these cases to the Committee on Safety of Medicines and have since discovered that there have been seven other cases reported to them regarding bowel ulceration, stricture, or perforation from Salupres therapy. Several of the doctors who reported these have written to me. I was interested to note that complications arose in one of these patients after being on therapy for six years, whereas Mr. K.L. had symptoms from the beginning of therapy, though of a rather vague nature. This would suggest that all patients receiving any form of potassium therapy should be consistently supervized for bowel disorders, with awareness that symptoms could arise at any stage. A warning to this effect does appear on all prescribing information on Salupres, and on all other of the firm's preparations containing potassium. Such a warning has appeared over the last few years in their literature, and this warning has been required by the Committee on Safety of Drugs (as it was then) since 1965 in all the promotional literature from the manufacturers.

One of the lessons which I have learned here is that one can become too familiar with a drug and be lulled into a sense of false security when using it repeatedly. Salupres is an excellent drug for the treatment of the milder forms of hypertension and I have used it as a drug of first choice for many years, because of its efficacy and apparent lack of side effects. A total of nine reported cases of intestinal complications is not very large when compared with the vast number of people who have benefited from this useful drug. A wide general awareness of the possibility of intestinal ulceration from potassium therapy should help to reduce the morbidity.

In this particular case I feel I tended to blame the patient for being a poor historian, to cover my failure to reach a diagnosis. Iatrogenic illness, by its very nature, often produces symptoms which do not fit any particular pattern. I feel that one should always be aware of this possibility, when presented with a problem which doesn't fit neatly into a recognized disease pattern and not hide in the assumed diagnosis of "functional" when a symptom is not fully understood.

General Hospital, Birmingham

Dear Brian,

I was interested to read your comments regarding Mr. K.L., and to hear of your other patient. When I looked back in the, by now voluminous, notes for a clue to allow us to make the diagnosis in retrospect, the very first document is your letter saying that he was on a mild hypotensive drug (Salupres). This is not a drug with which I am familiar and to my shame I did not check to discover what it was. Had I done so perhaps I might have made the diagnosis earlier, for many years ago I saw two cases of potassium stricture of the gut but they were much more acute and definite in their presentation than was this man. The important lessons for me are—always read the doctor's referring letter very carefully and always check on any drug therapy a patient may be having. It does no good to say "how instructive is this case," "how difficult it was to diagnose," and "all is well that ends well." We have wasted an awful lot of this man's time, the country's money and have caused him a lot of suffering by

failing to make an early diagnosis. I suppose that had we made the diagnosis at the very outset he might not have progressed to so tight a stricture that he required laparotomy. I presume that as soon as he had the first symptoms there was an ulcer in the gut with some hold-up and that subsequent tablets were arrested there and damaged the gut anew.

I see that you have reported this case to the Commitee on Safety of Medicines, and I think we should present it at a staff round in the hospital. Will you come along and take part in the case presentation?

We would like to thank Dr. K. Lovel (Committee on Safety of Medicines), and Dr. A. Andrew (Merck, Sharp and Dohme Ltd.), for their advice and help, and also to Dr. T. Brennan, Dr. F. J. Dunn, Dr. P. Elliott, Dr. B. D. Phillips, Mr. A. J. Newton, and Mr. D. I. Stirk for clinical details of their patients.

Glossary

B.P.	Blood pressure
Salupres	Containing hydrochlorothiazide, reserpine, and potassium chloride
E.S.R.	Erythrocyte sedimentation rate

Any Questions?

We publish below a selection of questions and answers of general interest

Oral Contraceptives after Cervical Cancer

Is there any evidence that oral contraceptives can reactivate cervical carcinoma which has been successfully treated with radiation?

No. Nevertheless there is a widely held view that a history of genital carcinoma should be regarded as a contraindication to the use of oral contraceptives. At the present time it cannot be stated with any certainty whether this view is correct or not.

Side Effects of Lithium Carbonate

Could lithium carbonate in an oral dosage of 1,000 mg daily give rise to two or three liquid and urgent stools on alternate days in a subject hitherto inclined to be constipated? Should the drug cause the urine to have an odour similar to disinfectant?

Gastrointestinal disturbance, including diarrhoea, is a recognized side effect of lithium therapy, particularly in the early weeks of treatment. Starting with a low dose and gradually increasing will usually avoid these and other early side effects. Lithium is rapidly absorbed and many side effects, including diarrhoea, often coincide with peak levels of lithium in the blood.[1 2] This is one reason why lithium carbonate should be given in divided doses throughout the day. A sustained release form of lithium carbonate is on the market (Priadel) and given once or twice daily obviates high peak levels of lithium in the blood and thus lessens the incidence of side effects. It would certainly be worth checking the serum-lithium levels to make sure that they are within acceptable limits. I have not heard or read of the urine smelling of disinfectant.

[1] Schou, M., *Journal of Psychiatric Research*, 1968, **6**, 67.
[2] National Institute of Mental Health, *Lithium in the Treatment of Mood Disorders*, Washington, U.S. Department of Health, Education and Welfare, 1970.

Indigestion from Drinking Water?

Do any substances occur naturally in drinking water, or enter drinking waters as chemicals used in its purification, which can cause indigestion in the consumer?

Indigestion is a vague term but I know of no substances which occur naturally in water which would give rise to it. Sodium chloride, if present in more than a very small concentration, will cause the water to taste salty, and iron, a common constituent of some waters, can impart a sharp, bitter flavour. Copper (used in the treatment of algae) can cause an unpleasant taste but in the concentrations used in water undertakings in this country is very unlikely to have harmful effects. No substances are added to water during purification which would cause indigestion.

Neurological Complications of Pertussis Immunization

Three weeks after a first triple antigen injection given at the age of 5 months a previously healthy baby girl showed signs of developmental slowing and began convulsive movements of head, shoulders, and arms. This progressed to true myoclonic infantile spasms. Diffuse cortical atrophy secondary to immunization with pertussis vaccine was diagnosed. Does this complication of pertussis immunization occur often and is there any way of preventing it?

The incidence of neurological complications of diphtheria-tetanus-pertussis vaccination is subject to speculation and controversy since the extent of under-reporting or misreporting of these reactions is not known, the reactogenic properties of pertussis vaccines may vary according to method of manufacture, and certain paediatric conditions of unknown aetiology, particularly hypsarrhythmia, or infantile spasms, occur in previously normal infants at approximately the age when they routinely receive D.T.P. vaccines.

Sir Graham Wilson in his review[1] of encephalopathies after pertussis vaccination refers to several published case reports but the incidence of such complications in Britain during the last six years has been in the region of one per million doses of vaccine. The condition described by the questioner—hypsarrhythmia or infantile spasms—usually occurs in previously normal infants under the age of 2 years and particularly between the ages of 6 and 12 months. It is not surprising therefore that about 50% of these infants received at least one dose of D.T.P. vaccine a few days, weeks, or months previously. This fact is sometimes regarded as evidence that the vaccine may have provoked the development of hypsarrhythmia or infantile spasms,[2 3] but no sound cause and effect relationship has been established, and the condition probably occurs with equal frequency in unvaccinated children. It is possible therefore that triple vaccination had no causal relationship with the development of this child's condition and that the incidence of this so-called complication of immunization is not much greater than in unvaccinated infants.

[1] Wilson, G. S., *The Hazards of Immunization*, The Athlone Press, University of London, 1967.
[2] Bower, B. D., and Jeavons, P. M., *British Medical Journal*, 1960, **2**, 1453.
[3] Ström, J., *British Medical Journal*, 1967, **4**, 320.