Letters to the Editor

Failure to demonstrate specificity of the morphological and histochemical changes in mucosa adjacent to colonic carcinoma

The failure of Isaacson and Attwood (1979) is to appreciate that transitional mucosa has been defined by us as a specific combination of histochemical and morphological changes. We, too, have found sialomucins in solitary ulcers, but the morphology is quite different from that of transitional mucosa, as their illustration shows. We, too, have found transitional mucosa with squamous and melanotic carcinomas of the anal canal (Greaves *et al.*, unpublished observations) but this in no way invalidates our hypothesis that transitional mucosa represents prepolypoid adenomatous neoplasia. On the contrary, it fortifies the concept since the anal canal is simply developing its own characteristic neoplasms. Furthermore, when we find transitional mucosa in a colostomy we expect to learn that the patient has had a rectal carcinoma removed, yet Isaacson and Attwood do not tell us about their cases. They would not be surprised to find an adenomatous polyp developing in the remaining bowel after a cancer had been excised, and we regard the anal canal equally part of the same field of action of putative carcinogens. Moreover, the secretory changes in transitional mucosa are not only quantitative, with increased sialomucins, but qualitative, with variable proportions of different types of sialic acids showing values between normal controls and tumours (Dawson *et al.*, 1978; Rogers *et al.*, 1978).

A. C. BRANFOOT
M. I. FILIPE
Department of Histopathology, Westminster Medical School, (University of London), 17 Horseferry Road, London SW1P 2AR

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Rogers, C. M., Cooke, K. B., and Filipe, M. I. (1978). Sialic acids of human large bowel mucosa: *o*-acylated variants in normal and malignant states. *Gut*, **19**, 587-592.

The authors have commented as follows:

Contrary to the assertion of Branfoot and Felipe, we fully appreciate their definition of transitional mucosa, and our 'failure' remains that of demonstrating its specificity as a premalignant change in colorectal mucosa. Mucosal morphology in solitary ulcer syndrome is quite variable, and our initial illustration of this was chosen to show the similarity to transitional mucosa (Figure). The editors of 'The Journal', however, requested the substitution of a more characteristic illustration. Both are from the same section. We are gratified to learn that Branfoot and Felipe have noted similar histochemical changes in solitary ulcer syndrome and have confirmed our findings with respect to anal melanomas and squamous cell carcinomas. The suggestion that the association of transitional mucosa with these anal tumours (and colonic lymphoma) reinforces the concept that it is a premalignant change is an original one but is not borne out by any statistical relationship between these various tumours, nor by analogy with other well-defined precancerous conditions of the colon, such as polyposis coli or ulcerative colitis. We cannot comment on the qualitative secretory changes alluded to by Branfoot and Felipe since these have not been sought in transitional mucosa not related to adenocarcinoma.

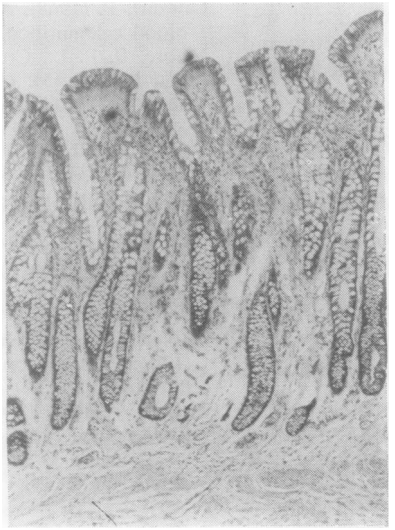

Figure *Mucosa from a case of solitary ulcer syndrome showing deepened branching crypts with enlarged goblet cells. Haematoxylin and eosin × 40.*

Our suggestion that transitional mucosa represents a secondary phenomenon, perhaps due to mechanical factors, is further supported by the recent paper of Rhatigan and Saffos (1979), who describe transitional mucosa in association with diverticular disease of the colon. Until more substantive evidence is produced we remain unconvinced that the changes characterised as transitional mucosa are premalignant, and still less that they represent 'adenomatous neoplasia'.

P. ISAACSON
P. A. R. ATTWOOD
Faculty of Medicine, Department of Pathology, Level E, South Laboratory/Pathology Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY

Reference

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Interpretation of serum total calcium

I have been involved previously, albeit in a very minor role, in the continuing saga of the 'corrected', or as it is now known 'adjusted' calcium (Sanderson, 1974). Once again, as a district hospital biochemist I find it difficult to know just who to believe. This time my dilemma concerns the precision of serum total calcium determinations required for diagnostic purposes.

Dr Payne and his colleagues, in their latest contribution to the subject (Payne

et al., 1979), base their findings on analytical coefficients of variation of 2% for calcium and of 3% for albumin, which they found at *normal* serum concentrations. These give a coefficient of variation for their 'adjusted' total calcium concentrations of 2·4% (Sanderson, personal communication). Now most of their data refer to patients whose calcium and albumin levels are far removed from normality, and yet no figures are given for the analytical coefficients of variation at these abnormal levels. One can, therefore, only assume that they have extrapolated their findings obtained in the normal to the abnormal situation without modification—a somewhat dangerous practice I would have thought! However, I feel that this uncertainty at least entitles me to say that the coefficient of variation for their 'adjusted' total calcium determinations in the patients they discuss is 2·4% +.

Now Mitchell (1978) states that 'for diagnostic purposes, calcium requires to be measured in serum with a high degree of precision and accuracy—(± 1% is generally considered to be desirable) — . . .'

In my opinion, there is a marked difference between 1% and 2·4% +, which leads me to ask just who is right?

C. SANDERSON
Biochemistry Department,
Airedale General Hospital,
Keighley, West Yorkshire BD20 6TD

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Sanderson, C. (1974). Correction of serum calcium measurements (Letter). *British Medical Journal*, **1**, 245.

The authors have commented as follows:

Mr Sanderson is worried that the analytical variation of calcium adjusted for albumin is greater than that of calcium alone. This is, of course, inevitable because the analytical variance of adjusted calcium is the sum of the analytical variances of total calcium and of albumin. However, diagnostic usefulness depends on the *overall* variation in calcium concentration in the groups that are being compared or in the individual in whom a change is being sought and not on the analytical variation alone.

Now, overall variance = biological variance + analytical variance. When calcium is adjusted for albumin there is a reduction in overall variance because there is a reduction in the biological variance which is greater than the increase in analytical variance. In the group of patients studied by Payne *et al.* (1973), the range of values for total calcium was 1·78-2·70 mmol/l whereas after adjustment for albumin the range was reduced to 2·25-2·60 mmol/l. Similarly, in our paper which Mr Sanderson criticises (Payne *et al.*, 1979), we showed that adjustment for albumin reduced the within-patient SD from 0·148 mmol/l to 0·100 mmol/l. We commented in our paper: 'These reductions in variability are the more striking because the values for adjusted calcium concentrations are based on independent single measurements of calcium and albumin, each of which has its own analytical error'.

R. B. PAYNE
Department of Chemical Pathology,
St James's University Hospital,
Leeds LS9 7TF
D. B. MORGAN
University Department of Chemical Pathology,
Leeds General Infirmary,
Leeds LS1 3EX

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Serum alkaline phosphatase in ankylosing spondylitis

As part of a survey of over 200 patients with ankylosing spondylitis attending the Centre for Rheumatic Diseases, Glasgow, the serum alkaline phosphatase (EC 3.1.3.1) activity was estimated. Details of the method have recently been published (Gardner and Scott, 1978). The mean value was found to be at the upper limit of the overall reference range for the method. Taking into account variation in enzyme activity in relation to age and sex, 28 patients (14%) were found to have raised enzyme levels. One of these patients had Paget's disease of bone.

More detailed biochemical investigations were carried out in nine of these patients with raised serum alkaline phosphatase activity. The enzyme was estimated in a different laboratory using the SMA 12/60 system (Morgenstern *et al.*, 1965) and was found to be still elevated in eight (the values ranged between 3% and 42% above the upper limit of the reference range; mean rise 21%). Serum alkaline phosphatase isoenzyme fractionation (performed by electrophoresis on both agarose and polyacrylamide gels) showed that the liver component was raised in all eight, and, in addition, one had a small elevation in the bone component. Serum γ-glutamyl transferase (EC 2.3.2.2) was raised in two to about twice the upper limit of the reference range, and three had high-normal or slightly raised results. Only one patient had marginally raised serum transaminases (aspartate transaminase EC 2.6.1.1 and alanine transaminase EC 2.6.1.2), and none had raised serum lactate dehydrogenase (EC 1.1.1.27) or bilirubin. Serum calcium corrected for albumin (Kennedy *et al.*, 1975) was normal in all eight, and serum phosphate was normal in seven and only marginally reduced in one.

Our results suggest that ankylosing spondylitis may not be as frequently accompanied by elevated serum total alkaline phosphatase as has been suggested by Kendall *et al.* (1973). Our findings of a raised liver fraction in all specimens from patients with raised total enzyme activity is also at variance with Kendall's finding of predominance of elevation of bone fraction. Only one of our patients had a slightly raised bone fraction in addition to the raised hepatic component. Our findings of raised γ-glutamyl transferase in two patients and border-line results in another three further support the contention that the biochemical abnormalities in these patients are mainly of hepatic rather than of bone origin. Golding (1973) has also stated that raised serum alkaline phosphatase in ankylosing spondylitis is not generally accepted to be the result of bony ankylosis.