

Another Milestone Passed

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I feel very honoured to have been invited to write an editorial – perhaps the first editorial – for this new journal. It is to be hoped that the *International Journal for Coeliac Disease* will flourish in becoming a focus for good research and reflection on what is now recognised as a fairly common disorder around the world.

I paused for a moment to reflect on how the *Oxford English Dictionary* defines ‘editorial’. It is an article, the Dictionary states, written for a journal, newspaper or magazine offering opinion on, or deliberations about, subjects of topical interest. Few would doubt that the pursuit of coeliac disease is a subject of intense topical interest. But it would be wrong to suppose that coeliac disease is merely of topical interest.

Many of us, whether physicians, laboratory technicians, scientists, or counsellors, will have spent a life-time in the pursuit of coeliac disease in the interests of those who have to live with this condition. When I first became interested in becoming a career gastroenterologist around 1966, I can recall how much of a struggle was presented to any newly-diagnosed coeliac patient by a gluten-free diet. The bread came in tins, was not always easy to get hold of, often turned mouldy, was a tasteless lump of matter that could hardly be cut into slices and was impossible to toast. It is a tribute to the food industry and its technology that the diet nowadays is a far more palatable experience.

Likewise, it is most important to acknowledge the striking growth of national groups, and the dedicated role which they so vitally play in the support of patients, through the guidance and counselling offered in helping them to make the dietary transition which is so vital for improved health and well-being. In September, many of us were able to take part in the 25th Anniversary of the founding of the European Consortium of Coeliac Societies in the impressive Tropical Disease Institute building in Amsterdam. Such social provision marks another significant milestone in the historical evolution of this condition.

When Samuel Gee first wrote the word “coeliac” in his notes at St. Bartholomew’s Hospital, London, in 1888, he could scarcely have imagined what eruptive revolution would take place during the ensuing century, and beyond. Neither, I suppose, would the Dutch paediatrician Wilhelm Dicke, c1950 and before, when he first came to realise, as another milestone, that it was the protein in wheat flour which is the agent injurious to the good health of affected individuals. A statement written too me by his widow, Mrs. Agaath Dicke-Schouten after the 50th Anniversary Meeting in Leiden for the publication of Dicke’s thesis, seems to grasp and epitomise the essential commitment that so many people show to coeliac patients and their families: “*He died after a well-spent life*

dedicated to sick children and trying to improve their health and their social situation in general”.

My personal interests in coeliac disease began in Professor Sir Christopher Booth’s department at the Royal Postgraduate Medical School of London, Hammersmith Hospital, and thence under Dr. Jerry Trier at Boston City University Hospital, Mass. I was very interested in microscopy as a means of uncovering tissue structure, but could not entertain thoughts of becoming a pathologist since I hated the prospect of having to dismember bodies as part of the post-mortem examination.

Yet, on returning to England, I was bothered by two issues: *First*, how could proper morphological comparisons be effected between normal and damaged intestinal mucosae? That was solved by the development of a computerised image-analysis system whereby all tissue volumes and cell enumerations were related to an invariant area of muscularis mucosae [1]; *Second*, following Fry’s recent (at the time) observations [2], how could apparently “normal” yet lymphocyte-infiltrated villi be related (if at all) to the classic flat mucosa upon which we had all been brought up?

Indeed, it was questionable whether these extreme lesions were, or even could be, part of a continuous process. The alternative was that they were unrelated and dependent on different aetiologies. It took several MD theses and a lot of work within my laboratory to discover how the mucosa changes from normal to the “flat” stage [3], the latter having held the stage for almost 40 years as the sole diagnostic criterion for coeliac disease. My fully-considered scheme was published in 1992 [4] and has now been widely used for over 20 years. Until that publication, no-one had apparently asked how the mucosa becomes damaged, and what antecedent steps might be recognisable as part of that progressive spectrum of change.

Professors Corazza and Villanacci complained [5] that I failed to accurately quantitate lymphocyte populations for each stage, and that Marsh II is not often observed.. They are entirely correct in their first assertion, but that was never my original intention. Their second observation may be the result of a temporal phenomenon – that the progress through Marsh II is rapid - and thus less frequently encountered. My scheme did not articulate the time-base of the progression, whether certain stages were more rapid than others, and whether all lesions invariably progressed forwards, remained static, or even regressed with time. The temporal evolution of the mucosal lesion still remains to be elucidated.

Next, we must begin to realise that the Oberhuber modifications [6] to the Marsh III stage are fairly useless: I agree with Corazza and Villanacci that they serve no useful practical value – histologically or diagnostically.

Those who persist in linking the Marsh classification to Oberhuber have either never read the paper, or if they have, their readings have been careless and uncritical. Oberhuber has no independent controls upon which to base his suppositions. Furthermore, his illustrated histological sections are poor and technically unsatisfactory. That they are meaningless can be revealed dramatically if Oberhuber's stages (a, b, c) are compared with those same stages as depicted by Dickson and colleagues [7]: it is quite evident that IIIa, b, c are far more imaginary than empirically real. The former was offered as a 'standardised framework for reporting', the latter as an 'update' for pathologists: from a structural perspective, both initiatives seem to be rather unfortunate. Finally, all those attempts to re-classify the mucosa, but which employ the Oberhuber categories, are likewise flawed and therefore of little use to the histopathologist.

A further detailed critique of Oberhuber is currently under review [8]. This paper continues by addressing the difficulties in understanding the complex, three-dimensional nature of the intestinal mucosa, and the relationship of progressive villous effacement to the upward growth of inter-villous ridges; the progressive amalgamation of groups of adjacent villi into mosaic platforms which lie at some considerable height above the true crypt-villus junction; the presence of large surface openings or "wells" which perforate the mucosal surface – and which confuse the interpretation of mucosal histology when viewed only with thin, two-dimensional sections –; and the fact that the upper crypts (and probably represented by the mosaic platforms) are villous, and not crypt-based, cellular territories. These considerations are of great importance in the analysis of mucosal histology: it seems to me that few people are bothered about them, or even understand them, these days.

We need far more attention paid to the earliest mucosal lesions (Marsh 0, I), especially those which histologically look "normal": these are logically part of the natural history of coeliac disease when viewed structurally, as I have recently tried to emphasise [9]. Importantly, they form part of the diagnosis upon which hangs the responsibility of recognising those patients and hence getting them started on a gluten-restricted diet. My personal view is that there is too much emphasis given solely to immunology and to the Marsh III lesion, while aspects of the cell biology of mucosal damage have lagged

considerably behind, to the detriment of increasing our understandings of the mucosal response to lymphocyte activation in this condition. And, who will be first to ask the question why, in certain circumstances, the mucosa fails to heal. Here, I would suggest, we need to invest much more thought towards the crypts and the molecular aberrations which, in inhibiting cell division, prevent mucosal regeneration.

There is much still to do and to understand. The horizon looks bright, although I doubt whether I shall be around, say 20 years hence, to make further commentary on those new advances and discoveries which undoubtedly will accrue.

But good luck to this *Journal*, and to those who serve it, that it may become a vehicle for publishing those undoubted future contributory gains in knowledge, and which will help in widening, still more, our collective understandings of a highly complex, yet intriguing, disorder.

References

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