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A Dialogue with Professor Michael N. Marsh

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Abstract In the accordance of readers, we are introducing a new chapter in Journal, which will consist in interview with one people. The chapter will appear as needed and the people will be select by editorial board. Professor Michael N. Marsh was invited for first interview and you can find a message from this interview here.

Keywords: *the first interview, journal questions, a great personality*

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1. Professor Marsh, thank you for aggreeing to be interviewed, and for your time in answering our questions. Journal readers are well familiar with your name within the field of coeliac disease research, so the usual introductory formalities, in your case, are unnecessary. But tell us, how did you first become interested in coeliac diease?

Well, that's easy. I had already decided that I preferred the metabolic side of medicine, rather than cardio-respiratory pursuits. I qualified in December 1962 from Magdalen College, Oxford University, and then worked as a junior house physician in the famous Nuffield Department of Medicine at the Radcliffe Infirmary, Oxford. That pushed my interests towards the bowel and blood in working with Leslie Witts, Sidney Truelove, John Badenoch and Sheila Callender who were important names at that time: (Another of my interests was that my future wife was one of Prof. Witts' nursing sisters on Willis ward).

But now, five plus years into my career, I applied to be registrar (senior intern) to Professor Sir Christopher Booth, who was Chief of Medicine at Hammersmith Hospital, otherwise known as the Royal Post-Graduate Medical School of London. Booth, who had previously demonstrated the ileal absorption of vitamin B_{12}, was now interested in coeliac disease, especially as the biopsy technique had recently revealed its characteristic mucosal changes in the small bowel.

That is what I became most familiar with, and after three years, I was then offered (competitively) a Medical Research Council (UK) Travelling Fellowship which I took up in Bob Donaldson's Gastrointestinal Unit at Boston City Hospital, Boston, Massachusetts in the Fall of 1970. There I worked with Jerry Trier who enjoyed worldwide expertise in mucosal anatomy. It was a fantastic place to be! There were about 40 departmental fellows from around the world who subsequently all went back to their origins in continuing GI work and setting up their own university departments. With Trier, I learned how to prepare specimens in Epoxy resin from which 1µm thin sections, cut with glass knives and stained with toluidine blue, could be examined with oil-immersion optics.

That technique, which was like using transmission EM at low power (1-2,000 diameters), would play an important role in my subsequent work in the Faculty of Medicine at Manchester University, UK. That was important for my career, because when I left Hammersmith Hospital for Boston, two massive problems worried me.

First, how to overcome the differences in morphology and thus apply valid, comparative morphometric measurements between normal and flat coeliac biopsies, and second, and perhaps most importantly (although its impact would only dawn on me some 20 years hence), was how the gluten-induced "infiltrated" lesions of dermatitis herpetiformis (described 1970) could possibly be linked – if at all - with the "classic" flat biopsy which had then been in play for over 20 years. All this would additionally involve the setting up of a computerised image-analysis system for precise mucosal measurement, and the realisation of a methodology through which I would be responsible in achieving those future aims.

2. What has been the most important finding in coeliac disease?

That rather sounds to me like a leading question! I think, undoubtedly, the introduction of the biopsy technique allowing fresh tissue from the small intestine to be taken from unanaesthetised human subjects. That really did open up the field. Before he died, I managed to telephone William Crosby at his American home, for two reasons: I wanted a photograph because no-one knew what he looked like (he did reply to that by saying his wife did!)

and for which he sent me an impressive slide of him dressed as Colonel, US Army Medical Corps, and secondly, because I wanted to know where his original capsule, engineered by Hans Kugler, was. His reply: 'It was stolen'. If he had agreed, I wanted to preserve the capsule in the Welcome Museum of the History of Medicine, London. He even sent me his copy of the US Army's collective Symposia (1958) on western (Caribbean) tropical sprue investigations in Haiti, the Dominican Republic, but predominantly Puerto Rica.

Ludwig Sollid's work on DQ2/8 specificities also figured highly in shaping the future pathways in celiac disease research. It seems as though the paper I published in Gastroenterology (1992) had some influence as well. Since then, there has been so much expansion in the laboratory side of things since 2000, as well as personnel involved, that it is difficult to pinpoint other specific advances. Clearly, the dissection of the immune response into adaptive and innate wings is now of vital importance – since those divisions and how they inter-act, are critical for further understandings of the immunopathology of coeliac disease, but may also permit some more sensible insights into what currently I think is a gobble-de-gook amalgam of words (Non-Coeliac Gluten Sensitivity). If you know what that means, you're a genius! Or, as I say to myself quietly – if only people would speak English properly.

3. Your article on the histopathology of coeliac disease is universally known. how did you come to realise it – was it a sudden idea, or did it evolve from your activities in the clinic or lab?

It came from various channels. Two of my earliest Research Fellows in Manchester, Richard Leigh and Duncan Loft both of whom were supported by Medical Research Council (UK) grants, carried out a series of oral challenges and showed the time-/dose- responsiveness of the IEL influx into epithelium, second the emerging and progressive crypt hypertrophy, and third the final flattening of the villi. That was a very long study.

Second, there were sporadic papers in the literature identifying patients with GI symptoms initially with a normal mucosa, but then later being shown to have a flat mucosa and thus being gluten restricted. There were two such patients in my Coeliac Clinic whom I wrote up.

Third, when Prof. Anne Ferguson visited our departmental labs in Manchester (c. 1980s), she told me of her joint experiments with Alan Mowat on mild GVH experiments with mice, in which there was a minimal doubling of crypt size but also a lymphocytic infiltrate into normal-sized villi (having previously shown with Tom MacDonald that T lymphocytes were essential for mucosal flattening to occur). That was exciting news.

Fourth, I got involved in another experiment with Tim Peters (also a Hammersmith colleague) who had now returned to London. We had both travelled to America with wives and children, although he worked on lysosomes in Christian de Duve's lab at the Rockefeller University, New York. Tim was first to demonstrate the increased permeability of severe mucosal lesions in celiac patients, suggesting a genetic basis. But I knew that Dick McConnell in Liverpool, interested in celiac genetics (many Irish immigrants from the previous century's potato famine), had scores of biopsies from relevant family members. I suggested repeating the experiments on family members *lacking* severe lesions, as there could be intermediate stages of increasing permeability. I would check the morphology of the patients enrolled. I think the first biopsy which I looked at revealed enormously infiltrated villi (in fact, Fig. 5 in the Gastroenterology paper of 1992): I nearly fell off my stool. Moreover, the correspondence with Ferguson's data was striking.

Together, all these factors impelled me to write, and offer the new proposals on mucosal progression..

So, there was no "heureka" (this Greek aorist *does* begin with a rough breathing!) moment, nor a flashing Damascene thunderbolt illumining the skies in some dark alleyway in downtown Manchester! As is usual, just the disciplined, careful recording and remembering of data and papers, and the ability to successfully put the odd thing or two together – as is the day-to-day humdrum nature of scientific life.

The text destined for publication in Gastroenterology was written in Adelaide while I was Distinguished Visiting Medical Scholar (1990) in David Shearman's Department at the Prince Albert Hospital. How nice to have some peace and time to write! It came almost 40+ years after the first severely-damaged biopsies came to light. My intent, as being the first composite review of coeliac disease at the time, was to overcome the patchiness of previous Coeliac Symposia, thus to project coeliac thinking into the molecular era by looking at possible HLA polymorphisms, likely gluten epitopes, demanding a systematic approach to coeliac lymphomas – as Theo Bayless had been doing at Johns Hopkins, and of course, describing the classification. It never dawned on me what a subsequent impact it would have: indeed, I had no reason to believe otherwise. I hand-drew the diagram (Figure 6 in Gastroenterology, 1992) on our kitchen table one rainy Saturday afternoon, just before submitting.

On reflection, the Classification certainly re-drew the diagnostic goalposts, so that over its 25 years of existence, possibly several thousands of people worldwide have been admitted to the diagnosis and treated, rather than being dismissed. To think that that could still be happening does, I think, still frighten me.

4. Do you think that coeliac disease research is stagnating, or, do you think there are specific groups providing significantly new information?

To take the first point: research into this area is by no means stagnating.

But there are several exciting lines of work which are transforming long-held views about this condition.

(a) I have already touched on the quest to settle the link(s) between the adaptive and innate arms of the immunoplogical response to gluten ingestion. There is much to do there.

(b) Interestingly, several groups have been working on the curious situation of Olmesartan-induced (and possibly

some of its cogeners) enteropathy and whether that, in some respects, mirrors a predominently innate-directed response to the drug. Once that is sorted there should be some interesting emergent concepts coming from that. And that might help shed light on the allied state of "gluten (non-coeliac) intolerance" and the extent to which this may represent some attenuated form of innate response, but which does not get sufficiently pumped-up to cause gluten sensitivity.

(c) Next, in view of gluten (non-coeliac) intolerance, there is a critical need to try and firm up the diagnostic criteria for those with minimal lesions, that is, Marsh 0 through II. Even recent guidelines from USA and UK are happy to dismiss (still!) those well-defined mucosal changes as "non-specific". Those called to write those guidelines should know better, since they do not provide much assistance to those in less privileged circumstances in deciding whether a patient is gluten-sensitised, or not. Far more (scientific) candour is necessary here, especially on the part of those who think they are leaders in the field!

(d) Next, regarding the innate response, there is still some way to go in determining how IEL become killer cells programmed to kill enterocytes. I do not favour the notion that (as it is sometimes put) "massive cell lysis" causes flattening. That is quite an amusing belief. First, there is a big concern as to how much destruction a single killer cell can perform in a day's work – and that is an important proviso which requires some attention. Second, removing the villous epithelium does NOT result in a flat mucosa, because it is supported by the inter-villous ridges, the mucosal microvasculature, and the basement membranes. To blindly claim that NKG2D killing is the sine qua non of mucosal flattening may turn out to be false, since that assertion seems not to be aware of much earlier research into those concepts which I have just mentioned. If the perpetrators of those views do not believe this, they should go and read the relevant literature – and maybe educate themselves. Third, how much structural evidence is there for "massive" cell destruction and loss. And, if that is the case, where in the mucosa is it happening?

(e) The trend in that thought-process leads us to the biological factors resulting in what I regard as the horizontally-based hypertrophic response to flattening as the mosaic plateaux are formed. This takes us far beyond the simplistic notions that killing a few enterocytes causes mucosal flattening. Here, there has to be widespread co-ordinated action between epithelium, basement membrane, the lamina propria, and the crypts, for this hypertrophic response to be finely engineered as flattening proceeds. And that is not a simple task. But it is heartening to see some groups introducing ideas surrounding gene clusters such as Hedgehog and Wnt factors as key players in this tissue drama being played out. We await some more extensive cell biology, to counter what at present is the overriding impact of immunologically-based approaches to the pathogenesis of coeliac disease.

(f) Briefly, I have been astonished at the surprising degree of iron deficiency manifested by those with Marsh 0 lesional pathology. My own surmise is that we must return to the enterocyte, determine the proportion of cells with damaged brush borders, since this is the initial molecular frontier which an iron ion must surmount before being transported into the cell, and thence onwards to the bone marrow. I think some hard work needs to be done on that issue to elucidate its cause.. And the preponderance of severe bone thinning is the proximate research project demanding some attention, too.

5. Do we need a world-based coeliac disease society, or are local (national) organisations adequate?

I am not fond of big organisations, and nationally-based organisations do well. Furthermore, there is a great need for local branches to deal with day-to-day clinical problems, have jamborees, and even teaching sessions. The local chapters are at the core of patient support and help. Let's continue in that way.

6. Do you think one day coeliac disease will be treatable – and not dependent on a gluten-free diet?

Well, this has been the pipe-dream of many on the way. It's a bit like wondering whether a robot will ever think and produce an original thought. I get the feeling this is not going to happen.

It is always a disaster telling a newly-diagnosed patient that the diet can no longer comprise wheat-based products. My own approach was to encourage these people – as far as possible - to use rice as a staple (which is pretty healthy) and to construct a new diet around that – with eggs, milk, fresh meat, fish, nuts and fruit. Many individuals were able to adapt, and adopt, this life-giving approach. Not only is this a positive approach – but it also absolves the rest of the family from having to go gluten-free.

Let me say just one more thing. I have always been intrigued by the fact that individuals with malabsorption could be overweight. The first reference I know comes from Cluysenaer's early book on malabsorption. Towards the end of my clinical years, I saw a lady one month after she started a gluten-free diet: that was always my practice so that if there were any difficulties they could be dealt with. Then I asked if her weight had gone up, and she said 'No – the reverse', remarking that her family had noted that her intake had fallen noticeably since dietary control was initiated. I think she previously had hyperphagia – similar to that following an intestinal resection – so that once her mucosa began to recover, her calorie intake fell proportionately. I have never seen any reference to Professor Ferguson's case (Gut) of a woman with the grossest morbid obesity sent for an jejunal blind loop procedure. A per-operative biopsy of jejunum revealed a flat mucosa!

7. And what do you do all day – and what of the future?

I do a lot of writing. There have been some odd tales floating around ("off his head": "getting a bit soft": "got ordained" etc). I had been thinking about retirement before I actually resigned from faculty duties at Manchester University. Indeed, Marsh's Rule states that you need to

get your retirement plans into shape long before you get the golden handshake. My wish was to get back to my schoolboy Greek (which in subsequent years, always guided the way in which I wrote English and for which I have a fierce regard). But I was always fascinated by Hebrew – perhaps the characters as well as the language. But having found no primary degree courses for both at any UK university, I opted to read the Oxford Theology degree, while simultaneously joining an informal Greek reading club, and hiring a private tutor to teach me Hebrew. Having then graduated, I returned to Magdalen College, Oxford to begin writing a D.Phil thesis on the neuropathological and theological aspects of out-of-body and near-death experiences. This was subsequently published in the prestigious Oxford Theology Monograph Series (OUP, 2010).

Since then, in addition to my DPhil, I have published two other books, the most recent (IFF Books, New York, 2015) concerned with being human – but observed from a kind of clinical background which sensitises any doctor to the wretched plight of so many, forced by uncontrollable circumstance, to bump along on the bottom. I have also written about 20 papers on the ethical and moral outcomes of current medical practice, regarding disability and being disabled by others' inhumane attitudes; abortion and infanticide; and the legal spectre of lawfully-conditioned assisted suicide – and euthanasia.

Writing within the "humanities" oevre is a sobering moment, I can tell you. I am just battling with Humanities over a MS for which 14 faculty-appointed reviewers refused to review. My favourite came out last year in the European Review, entitled: "Hey! What's that gorilla doing over there?" Read it and literally have your eyes opened.

All this activity helps me in not having to stay in bed every day.