Correspondence

Duodeno-jejunal adenocarcinoma and coeliac disease

We read with interest the report by MacGowan *et al* of two cases of duodeno-jejunal adenocarcinoma representing a first presentation of coeliac disease.¹ We have recently encountered a similar case of coeliac disease presenting initially as a periampullary adenocarcinoma, in which changes of severe villous atrophy and an associated lymphocytic gastritis were present in the Whipple's resection specimen.

A 42 year old woman presented with symptoms and signs of intermittent obstructive jaundice. Endoscopic retrograde cholangiopancreatography revealed a duodenal tumour, biopsies of which confirmed adenocarcinoma. Pancreaticoduodenectomy and cholecystectomy were performed and histology confirmed a poorly differentiated periampullary adenocarcinoma with four positive lymph nodes. In addition, histology of the duodenal mucosa not involved by tumour showed severe villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes typical of untreated coeliac disease. Histology of the antral portion of the resection specimen showed features of an active lymphocytic gastritis.

The patient subsequently developed profuse malabsorptive diarrhoea with reduced levels of vitamin B12 and folate. She was put on a gluten free diet and significant weight gain ensued. Repeat distal duodenal and gastric biopsies have shown a marked improvement in villous architecture and resolution of the lymphocytic gastritis.

Of particular interest in this case was the additional finding of a lymphocytic gastritis within the antral gastric component of the Whipple's resection specimen. It is recognised that there is a significant association between coeliac disease and both lymphocytic colitis² and lymphocytic gastritis,³ possibly representing a manifestation of gluten sensitivity at different levels of the gastrointestinal tract. Although it is recognised that the changes of lymphocytic gastritis may be focal, it is possible that resolution of the lymphocytic gastritis in this case represents a response to gluten free diet and this phenomenon merits further study.

This case is an additional example of coeliac disease presenting with a small bowel carcinoma and the findings further highlight the association between coeliac disease and lymphocytic gastritis. The possibility of occult coeliac disease should be considered in patients presenting with small bowel carcinoma or showing the gastric biopsy appearances of lymphocytic gastritis.

C H MASON
A A DUNK

Departments of Histopathology and Gastroenterology,
Eastbourne District General Hospital,
Kings Drive, Eastbourne,
East Sussex BN21 2UD, UK

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Diagnosis of thin melanoma

I read with interest Professor Mooi's editorial "Diagnosis of thin melanoma".¹ His comments included a hypothesis arguing for the development occasionally of melanoma from the superficial dermal component of a melanocytic lesion. This may well be theoretically plausible but in practice the number of primary cutaneous invasive melanomas without an epidermal or junctional component is vanishingly small. This by no means refutes the hypothesis that actual acquisition of aggressive features of melanoma arises in stages including an intermediate superficial dermal invasion without metastatic potential (microinvasion).^{2,3} However, it is not clear how this can be used against the concept of melanocytic intraepidermal neoplasia (MIN).⁴ MIN was not a concept devised to explain the biological sequence of melanoma development, it was a response to an unnecessary diagnostic dilemma based on the excessive numbers of diagnostic categories applied to preinvasive atypical melanocytic lesions.

The term MIN has been demonstrated to reduce diagnostic discordance and at the same time remove the label melanoma (in situ) from a number of lesions that, if excised, are known not to present subsequent problems of recurrence or metastasis.

Professor Mooi is right that small atypical melanocytic lesions are common and the difficulty for pathologists is identifying those which have an entirely favourable prognosis. The CRC group believed that if such cases could be confidently recognised it would be beneficial to refer to them in a different way.

Professor Mooi makes the wrong assumption that MIN does not apply to junctional naevi. The papers describing MIN^{3,4} were definitely intended to include both junctional and compound melanocytic lesions. His other criticisms of the words intraepidermal and neoplasia are appropriate. It could be argued that the small number of cases showing adnexal extension of melanocytes makes the term intraepithelial more exact.

The term neoplasia applies to most melanocytic tumours and was chosen to make the term more memorable by analogy with CIN rather than for semantic accuracy. The term melanocytic intraepithelial neoplasia in its entirety refers to melanoma in situ and severely dysplastic melanocytic naevi, to emphasise the futility of attempting to separate them. I am grateful for the generally supportive comments in the rest of the editorial.

M G COOK
Chairman, CRC Melanoma Panel,
Department of Histopathology,
The Royal Surrey County Hospital,
Guildford, Surrey, UK

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- CRC Melanoma Pathology Panel. A nationwide survey of observer variation in the diagnosis of thin cutaneous malignant melanoma including the MIN terminology. *J Clin Pathol* 1997;50:202-5.

Professor Mooi comments:

I thank Dr Cook for his interest in my recent editorial, which commented on the CRC Melanoma Pathology Panel paper on thin cutaneous melanoma.

Two points need, perhaps, further clarification. My problem with the term MIN being applicable to junctional naevi is the fact that it is applicable to all junctional naevi, regardless of the presence or absence of atypia. Thus, the distinction between the categories "benign" and "MIN with no microinvasion", as evident from fig 1 in the CRC Panel paper, would not be entirely appropriate.

Perhaps more important than this question of terminology is the more basic biological issue of the concept of invasion in melanocytic tumours. The remarks made in my editorial were not aimed specifically at the CRC Panel's paper. My point can be summarised as follows: as the precursor lesion of invasive melanoma is most commonly a naevus with an intradermal (as well as an intraepithelial) component, the pathogenesis of some melanomas is bound to be different from that of epithelial neoplasms, unless we assume, without proof, that the intradermal component of the naevus is always an innocent bystander, and never plays a role in the pathogenesis of the tumour. Perhaps we have to reconsider the current dogma, which dictates that cutaneous melanoma always arises in the epidermis and that its presence in the dermis results from invasive growth. The fact that the number of purely intradermal primary melanomas is "vanishingly small" does not prove that the intraepithelial component was always first, and the intradermal component develops as a result of "invasive growth".

I feel that we are well advised to exercise some caution when using the concept of early malignancy and early invasion of epithelial neoplasms as the template on which we mould our terminology of melanocytic neoplasms. We have discontinued the use of the term melanocarcinoma, commonly used a few decades ago, but in some ways our concept of melanocytic tumours continues to be related to epithelial neoplasms to a degree that is not really supported by solid data.

As indicated above, this is not a criticism specifically aimed at the paper by the CRC Panel, it is aimed at most of us, including myself! However, I am sure we all agree that in science it is never too late to reconsider critically one's beliefs and assumptions.

MIN terminology

"Rolling stones gather no moss". Similarly, despite increased verbal support for the term melanocytic intraepidermal neoplasia (MIN), the subject has received little formal published appraisal. For this reason, Professor Mooi's editorial on the diagnosis of thin melanoma is of particular importance.¹ As-tutely, he highlights several significant conceptual and practical drawbacks associated with the term MIN. I share his overall reservations and propose that other considerations should be added to his list.

First, it is essential that adoption of the term MIN only follows extensive international discussion and agreement. The United Kingdom must not go it alone and become isolated.

Second, the scientific and diagnostic basis for radial and vertical growth phases in melanoma must be established beyond rea-

sonable doubt. Personally, I find it hard to believe that the invasive potential of melanoma is reliably predicted by the width of dermal nests of melanocytes.²

Third, I realise that Dr Cook has not proposed a subdivision of MIN that also incorporates low grade changes.² To many histopathologists, however, this will be a natural temptation in view of similar usage in other types of intraepithelial neoplasia. The incidence of MIN would then increase dramatically and stand the chance of losing credibility by becoming a depositary for many minor abnormalities.

Finally, as the epidemiological aspects of melanoma are of crucial public health importance, reports will have to contain both old and new terminology into the foreseeable future.

As emphasised by Professor Mooi, the CRC Panel's study is an important analysis of observer variation in the diagnosis of thin cutaneous melanoma.³ One wonders, however, what results would have been achieved by a control group of general histopathologists using traditional atypical (dysplastic) melanoma terminology and enforced reading of an acknowledged reference source, such as the Armed Forces Institute of Pathology, *Melanocytic tumours of the skin fascicle*.⁴

DAVID SLATER
Rotherham Hospitals NHS Trust,
Moorgate Road,
Rotherham S60 2UD, UK

- 1 Mooi WJ. Diagnosis of thin melanoma [editorial]. *J Clin Pathol* 1997;50:179-80.
- 2 Cook MG, Clarke TJ, Humphreys S, et al. The evaluation of diagnostic and prognostic criteria and the terminology of thin cutaneous malignant melanoma by the CRC Melanoma Pathology Panel. *Histopathology* 1996;28:497-512.
- 3 CRC Melanoma Pathology Panel. A nationwide survey of observer variation in the diagnosis of thin cutaneous malignant melanoma including the MIN terminology. *J Clin Pathol* 1997;50:202-5.
- 4 Elder DE, Murphy GF. *Atlas of tumour pathology. Melanocytic tumours of the skin*. 3rd series. Fascicle 2. Washington: Armed Forces Institute of Pathology, 1991.

Dr Cook and colleagues comment:

Dr Slater makes several points in his letter about our paper and the use of the term melanocytic intraepidermal neoplasia. It may be worthwhile reiterating the processes by which the CRC Melanoma Pathology Panel came to suggest MIN for consideration. The CRC study of melanoma in pigmented lesions identified a wide discrepancy between the centres participating in the diagnosis of thin melanomas. The CRC Panel tried to identify the causes and solutions to this problem but only succeeded in providing a modest improvement in concordance. The possible implication suggested that the difference between dysplastic melanocytic lesions and melanoma in situ was not sharp and that they were not biologically distinct. Furthermore, as they were not managed differently the panel considered the need to continue to recognise them as separate entities. A term such as "melanocytic dysplasia-melanoma in situ spectrum" might have been used but an alternative—MIN—was considered more usable, and analogies with CIN were emphasised. Professor Mooi pointed out that "intraepithelial" would be more precise than "intraepidermal" and we would not argue with that. He also considered the term neoplasia to be too inclusive but we would

argue that it can have a more specific meaning when used in the context as we have defined it.

Professor Mooi has indicated that he does not personally value MIN highly because he avoids the diagnostic dilemma by hardly ever making the diagnosis of melanoma in situ, and he therefore does not have a problem in distinguishing it from dysplastic lesions (personal communication, Professor Mooi, 1997). His idea that the origin of some melanomas may be from the dermal component is interesting but not in conflict with MIN. However, it does question the use of microinvasion as an appropriate term and clearly there is much work to be done in validating either theory.

As far as Dr Slater's comments are concerned, we would like to emphasise that we put forward the MIN terminology for consideration as a possible solution to a demonstrable problem. We have tested its acceptability with a national survey but accept that further discussion and agreement is necessary before it could be a formal recommendation.

Dr Slater is also broadening his aim to include the validity of the growth phase concept of Clark *et al.*¹ We agree that this interesting theory does need more published support before it can become firmly accepted. His suggestion of the inevitable subdivision of MIN is completely against the rationale for introducing the term and we cannot accept this argument.

The existing epidemiological data for melanoma is based on current terminology and is therefore flawed, hence the need for the CRC Pathology Panel study in the first place. It is accepted that clarification of that data will take many years but it will be necessary whatever terminology is adopted.

The most important results from the nationwide survey highlight the need for more reliability in the recognition of melanoma and related lesions. This problem needs to be urgently addressed, as the detection of thin melanomas and borderline lesions has been rising rapidly.

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Serum CagA antibodies in asymptomatic subjects and patients with peptic ulcer

We read with great interest the paper by Graham *et al.* in which, although different methodologies were used, the authors failed to find a significant association between CagA seropositivity and peptic ulcer disease or increased antral inflammation in a North American population.

We would briefly like to mention our previous experience about the patterns of antibody response to *Helicobacter pylori* infection in patients with chronic renal failure.² A group of 51 patients with different degrees of chronic renal failure was studied: histology of gastric specimens was carried out according to the Sydney's system, and serum antibodies to CagA were investigated by western blotting. The prevalence of infection was 76.4% and patients infected by *H pylori* had a greater activity of gastritis than non-infected patients ($p < 0.0001$). However, patients infected by CagA positive strains of *H pylori* did not have

a greater activity of gastritis than those infected with CagA negative strains ($p = 0.540$). No significant correlations were found with other histological features such as gastric atrophy, chronic inflammation, and intestinal metaplasia.

These results raise some questions about the pathogenetic mechanism of *H pylori* infection. Finding a specific or a unique virulence factor of infection should lead us to select patients for more specific treatment and, among the virulence factors considered, CagA has been suggested as one of the most important.³

However, the work of Graham *et al.* seems to exclude this, at least for the North American population. Moreover, our findings, obtained in patients with chronic renal failure, seem to confirm that CagA seropositivity is not necessarily related to increased antral inflammation, suggesting that the gastric microenvironment present in the stomach of these patients could interfere with the pathogenetic mechanism of *H pylori* infection.

These findings underline that clinical infectious disease usually represents an interplay between the bacteria and the host and that the "variable host" should receive more attention. We believe that further studies in a well defined population could help clarify the exact pathogenetic mechanism of *H pylori*.

F FRAGGETTA
E VASQUEZ
Istituto di Anatomia Patologica,
Università di Catania,
Via Biblioteca n° 4,
95124 Catania, Italy

A GRANATA
P FATUZZO
F RAPISARDA
Divisione Clinicizzata Nefrologia Chirurgica
N FIGURA
Istituto di Patologia Speciale Medica,
Università di Siena, Italy

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- 2 Rapisarda S, Figura N, Granata A, Vasquez E, Fraggetta F, Randone S, et al. Degrees of gastritis and patterns of antibody response to *H. pylori* infection in patients with chronic renal failure [abstract]. *Gut* 1996;38(suppl 2):A53.
- 3 Peek RM, Miller GG, Tham KT, Perez-Perez GI, Zhao X, Atherton JC, et al. Heightened inflammatory response and cytokine expression in vivo to cagA+ *Helicobacter pylori* strains. *Lab Invest* 1995;73:760-70.

Inflammatory pseudotumour and Rosai-Dorfman disease of soft tissue

We read the recent article by Govender and Chetty¹ with great interest. The authors report the presence of a soft tissue lesion showing combined histological and immunophenotypical features of Rosai-Dorfman disease (RDD), and an inflammatory pseudotumour. They conclude that there may be a continuum between the two entities, with RDD representing the early histiocytic lesion and inflammatory pseudotumour the later (myo-) fibroblastic lesion. The alternative hypothesis is that aberrant cytokine expression in an inflammatory pseudotumour results in transformation of histiocytes.

The authors did not mention whether investigations for mycobacteria were performed. We have recently observed the