pylori, may cause chronic active gastritis. Like *C. pylori*, the number of organisms can probably be suppressed but complete eradication will probably be difficult. Was case 2 endoscoped and assessed symptomatically at a later date? If so, organisms may well have been detectable. Dr Logan and his colleagues may be right that "*Gastrospirillum hominis*" causes non-ulcer dyspepsia, but larger studies are needed, and I think it is still premature to draw conclusions from single patient histories.

Lack of significant effect of therapeutic propranolol on measurable platelet function in healthy subjects

Pamphilon and colleagues have shown that propranolol, a non-selective β blocker, does not significantly inhibit platelet function when therapeutic doses are administered to healthy subjects.¹ They suggest that a different response might be obtained in patients with cardiovascular disease and hyperactive platelets. Some additional comments may be of interest.

The authors discuss the possibility that β blockers exert their action in situations where circulating catecholamine concentrations are very high. We assessed the effect of acute hypoglycaemia (during insulin stress tests) on various metabolic and haemostatic variables in healthy subjects who had been given either placebo, nadolol, or propranolol, orally, for 10 days.² These non-selective β blockers significantly inhibited some catecholamine-mediated effects (hypokalaemia; a rise in factor VIII), but only propranolol had a marginal inhibitory effect on platelet aggregation.

In another study we found that platelet aggregation induced by adrenaline was significantly decreased in samples obtained from patients with a diagnosis of acute myocardial infarction or ischaemic heart disease who were taking β blockers when compared with a similar group of patients not taking such medication.³ Beta blockade may, indeed, be associated with platelet antiaggregatory effects but that these may only be elicited in conditions associated with pronounced platelet hyperaggregability such as myocardial infarction and ischaemic heart disease.³

There are also important methodological considerations in assessing the effect of drugs on platelet function. For example, whole blood platelet aggregometry (impedance or "free" cell count techniques) allows the effects of drugs on platelet, red, or white cell interactions to be measured. This has occasionally resulted in a better definition, even at lower doses, of the effects of several drugs, such as nifedipine, dipyridamole, heparin and ethanol, on platelet aggregation.⁴ Mean platelet volume, measured by very sensitive techniques (using a Coulter C256 channelyser), may also be another very sensitive method to assess the effect of a variety of agents on platelets.⁵

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1 Pamphilon DH, Boon RJ, Prentice AG, Rozkovec A. Lack of significant effect of therapeutic propranolol on measurable platelet function in healthy subjects. *J Clin Pathol* 1989;42:793-6.

2 Mikhailidis DP, Barradas MA, Hutton RA, Jeremy JY, Sabur M, Dandona P. The effect of non-specific β -blockade on metabolic and haemostatic variables during hypoglycaemia. *Diabetes Res* 1985;2:127-34.

3 Mikhailidis DP, Barradas MA, Mier A, et al. Platelet function in patients admitted with a diagnosis of myocardial infarction. *Angiology* 1987;38:36-45.

4 de Almeida PJ, Pires JGP, Marquezini AJ, Barradas MA, Mikhailidis DP. Platelets, vessels and coagulation: an overview of basic mechanisms with special reference to drug action. *J Drug Develop* 1990 (in press).

5 Whitworth NH, Barradas MA, Mikhailidis DP, Dandona P. An investigation into the effects of bacterial lipopolysaccharide on human platelets. *Eur J Haematol* 1989;43:112-9.

Dr Pamphilon et al comment:

The comments of Barradas and Mikhailidis are of interest and point to the relevant mechanism whereby β blockers may exert a beneficial effect in patients with myocardial infarction and ischaemic heart disease—that is, modulation of platelet hyperaggregability in susceptible subjects.¹ The observation that propranolol but not metoprolol enhances platelet aggregatory responses to adrenaline remains unexplained.² Thus it seems likely that blockade of the effects of high concentrations of circulating catecholamines is of central importance. We did not observe significant changes in the mean platelet volume in either group of subjects using the Coulter S Plus 4 rather than the Coulter C256 channelyser.

1 Mikhailidis DP, Barradas MA, Mier A, et al. Platelet function in patients admitted with a diagnosis of myocardial infarction. *Angiology* 1987;38:36-45.

2 Winther Hansen K, Klysner R, Geisler R, Bjerra Knudsen J, Glazer S, Gormsen J. Platelet aggregation and beta-blockers. *Lancet* 1982; i:224-5.

Leukaemic phase of mantle zone (intermediate) lymphoma: its characterisation in 11 cases

In his parody of lymphoma classifications a distinguished editor of the *Journal of Clinical Pathology* reflected the confusion and cynicism of the average pathologist at the perceived hair-splitting of the lymphomaniacs in their attempts to categorise non-Hodgkin's lymphomas.¹ The confusion over the classification of low grade non-Hodgkin's lymphomas is well illustrated by the report on the leukaemic phase of mantle zone (intermediate) lymphoma by Pombo de Oliveira et al.² The category of intermediate cell lymphoma was first proposed by Berard et al.^{3,4} It was noted that, "these tumours contain some lymphocytes resembling those of well differentiated lymphocytic tumours and some atypical cells more closely resembling the poorly differentiated lymphocytes of nodular or follicular lymphoma".⁵ It is now widely accepted that lymphocytic lymphoma of intermediate differentiation (INT) and mantle zone lymphoma (MZL) are the same tumour, perhaps at different stages of evolution,⁶ and Jaffe et al have proposed that MZL should be the preferred term.⁵

The category of centrocytic lymphoma was introduced into the Kiel classification to describe a diffuse lymphoma of small, slightly irregular lymphoid cells that were originally thought to be of follicle centre derivation (hence the name centrocyte).⁷ Subsequent studies have shown that centrocytic lymphoma is a distinct entity, clinically, morphologically, and phenotypically distinct from follicle centre cell lymphoma.^{8,9} It is unfortunate and confusing that the term "centrocytic lymphoma" is still applied to this tumour even after it has been shown not to be of centrocyte origin.

Many authors have suggested that INT/MZL is the same entity as centrocytic lymphoma.

In a review of INT/MZL, Jaffe et al concluded that this tumour, "clinically, morphologically, and immunophenotypically appears virtually identical to centrocytic lymphoma of the Kiel classification".³ Pombo de Oliveira et al seem to have retreated slightly from that position and conclude that, "centrocytic lymphoma and INT are clearly closely related morphologically and phenotypically but may not be entirely interchangeable pathological entities".² The authors further state that, "perhaps the application of molecular, genetic, or cytogenetic markers may allow such cases to be appropriately classified in future". In fact, cytogenetic studies suggest a close relation between INT and lymphocytic lymphoma.¹⁰

It is my opinion that the recognition of INT based on the finding of a mixture of cells with round and cleaved nuclei is flawed. It has been recognised for years that quite apart from biological variability, fixation and processing artefacts can induce considerable variation within a single neoplasm. Lymphocytic lymphomas and centrocytic lymphomas have been well described and defined histologically. It can, however, be difficult to separate these neoplasms on the morphology of the lymphoid cells alone, particularly in suboptimally fixed tissues. There are, however, many other features that assist in the differentiation of these two neoplasms, perhaps the most reliable being the identification of paraimmunoblasts which are always present in variable numbers in lymphocytic lymphomas and never found in centrocytic lymphomas. On the basis of this criterion, figs 7 and 8 of the paper by Pombo de Oliveira et al² show a centrocytic lymphoma and figs 10 and 11 a lymphocytic lymphoma. Clearly, the status of INT will not be resolved until a more reliable means of identification, other than variability of nuclear shape, is used to select cases for study.

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1 Kay HEM. Classification of non-Hodgkin's lymphomas. *Lancet* 1974;i:586.

2 Pombo de Oliveira MS, Jaffe ES, Catovsky D. Leukaemic phase of mantle zone (intermediate) lymphoma: Its characterisation in 11 cases. *J Clin Pathol* 1989;42:962-72.

3 Braylan RC, Jaffe ES, Berard CW. Malignant Lymphomas: current classification and new observations. In: Sommers SC, ed. *Pathology annual*. Volume 10. New York: Appleton-Century-Crofts, 1975:213-70.

4 Berard CW, Jaffe ES, Braylan RC, Mann RB, Namba K. Immunologic aspects and pathology of the malignant lymphomas. *Cancer* 1978;42:911-21.

5 Jaffe ES, Bookman MA, Longo DL. Lymphocytic lymphoma of intermediate differentiation-mantle zone lymphoma: A distinct subtype of B-cell lymphoma. *Hum Pathol* 1987;18:877-80.

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7 Tolksdorf G, Stein H, Lennert K. Morphological and immunological definition of a malignant lymphoma derived from germinal centre cells with cleaved nuclei (centrocytes). *Br J Cancer* 1980;41:168-82.

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9 Harris NL, Nadler LM, Blank AK. Immunohistologic characterisation of two malignant lymphomas of germinal center type (centroblastic/centrocytic and centrocytic) with monoclonal antibodies. Follicular and diffuse lymphoma of small cleaved type are related but distinct entities. *Am J Pathol* 1984;11:262-72.

- 10 Weisenburger DD, Sanger WG, Armitage JO, Purtillo DT. Intermediate lymphocytic lymphoma: Immunophenotypic and cytogenetic findings. *Blood* 1987;69:1617-21.

Drs Jaffe and Catovsky comment:

Professor Wright is critical of our report on the leukaemic phase of intermediate mantle zone (INT/MZL) lymphoma. The main object of our paper was to describe the peripheral blood features of this lymphoma in its leukaemic phase and to draw a distinction from chronic lymphocytic leukaemia; not to discuss the relation of INT/MZL and centrocytic lymphoma. We are confident that his comments and this letter will clarify any remaining confusion.

We have not departed from the view proposed by Jaffe *et al* that INT/MZL is essentially the same entity as centrocytic lymphoma.¹ As the article by Jaffe *et al* was an editorial comment and opinion piece, however, we felt that some caution was warranted regarding this conclusion. While the term INT/MZL as we use it would encompass all lesions recognised as centrocytic lymphoma, we are not sure that the converse would apply for those pathologists who use the category "centrocytic"—that is, some cases which we would diagnose as INT/MZL others might not feel compatible with the diagnosis of centrocytic as they use it. Thus we did not wish to conclude that these lesions are "entirely interchangeable pathologic entities".

We agree with Professor Wright that varying degrees of nuclear irregularity may be difficult to detect in routinely processed paraffin wax sections, particularly if they are processed in different laboratories with different fixatives and sectioning techniques. We would also agree that the lymph node shown in figs 9-11 would not be classified as INT, and that the overall features are more compatible with the diagnosis of SLL/CLL. These cases (12-16) were classified by us as small lymphocytic with cleaved cells, rather than INT (see table 3). As we noted in our description, the presence of pseudofollicular growth centres and paraimmunoblasts ("larger lymphoid cells with prominent central, often eosinophilic, nucleoli") were the principal criterion in this distinction. Thus we would agree with Professor Wright that figs 7 and 8 show a centrocytic lymphoma and figs 10 and 11 a small lymphocytic lymphoma. When relying solely on the peripheral blood film, however, it may be difficult to distinguish INT from small lymphocytic lymphoma as the paraimmunoblasts do not usually circulate in large numbers. Cases 12-16 were included in the study because in the peripheral blood film they were indistinguishable from INT and would have been classified in the lymph nodes as INT using the criteria of Weisenburger (personal communication).²

We stated that the application of molecular genetic or cytogenetic markers might allow such cases to be appropriately classified in the future. We still believe this statement to be correct. While the paper by Weisenburger *et al* does suggest a close relation between INT and lymphocytic lymphoma,² we believe those authors reached that conclusion because they included within INT cases similar to those illustrated in figs 9-11. Thus while Professor Wright and we both recognise that cases 12-16 are not appropriately included within INT/MZL, this opinion may not be universally held. In fact, we would conclude that the study by Weisenburger supports the

conclusion that we reached—namely that cases 12-16 are more appropriately included within small lymphocytic lymphoma/CLL and not INT/MZL. Hopefully, further studies will help bear out this conclusion, providing support for the distinction between INT (cases 1-11) and small lymphocytic lymphoma with cleaved cells (cases 12-16).

- 1 Jaffe ES, Bookman MA, Longo DL. Lymphocytic lymphoma of intermediate differentiation-mantle zone lymphoma: A distinct sub-type B-cell lymphoma. *Hum Pathol* 1987;18:877-80.
- 2 Weisenburger DD, Sanger WG, Armitage JO, Purtillo DT. Intermediate lymphocytic lymphoma: Immunophenotypic and cytogenetic findings. *Blood* 1987;69:1617-21.

Lupus cofactor phenomenon

I read with interest the recent paper by Mathey *et al* about a case of familial antiphospholipid syndrome.¹ The authors stated that the lupus anticoagulant could not be confirmed in the father, although the APTT did not correct with normal plasma. The results showed that the addition of normal plasma further prolonged the APTT by five seconds, making it seven seconds prolonged. This is an example of the lupus cofactor phenomenon.

Although the exact nature of this cofactor is unknown, it cannot exert its effects unless the lupus anticoagulant is present.² This is indirect confirmation that the lupus anticoagulant is present in this patient. The fact that the dilute Russell's viper venom time (DRVVT) was equivocal does not change this conclusion as a recent study has shown that the DRVVT will not detect all lupus anticoagulants.² Perhaps a further confirmatory test would have been useful for this patient—a tissue thromboplastin inhibition test or platelet neutralisation procedure.

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- 1 Mathey F, Walshe K, Machie IJ, Machin SJ. Familial occurrence of the antiphospholipid syndrome. *J Clin Pathol* 1989;42:495-7.
- 2 Samuel CLL, Oldmeadow MJ, Howard MA, Firkins BG. Comparisons of laboratory tests used for identification of the lupus anticoagulant. *Am J Haematol* 1989;30:213-20.

Dr Mackie et al comment:

We stated that the APTT was performed as a screening test, using control plasma, patient plasma, and a 50/50 mixture, and that the presence of a lupus anticoagulant was confirmed by a more specific technique. The APTT alone is generally not suitable for determining the presence or absence of lupus anticoagulant because even if a sensitive reagent is used, it is not specific, and may be influenced by factor deficiency, increased concentrations of coagulation factors, as well as by various inhibitors, including: antiphospholipids, antibodies against coagulation factors, and heparin.

We used the DRVVT as a confirmatory test with a platelet neutralisation procedure, using freeze-thaw, lysed, washed normal platelets. Tissue thromboplastin inhibition tests are less sensitive and give false negative results in many patients, especially those with IgM lupus anticoagulant.² Most recent comparisons of lupus anticoagulant tests have found that the DRVVT and kaolin clotting times are the most sensitive and reliable, although no single test has a 100% detection

rate. Unfortunately, it is not always possible to perform more than one of these tests.

In the family described the APTT did not correct in the father, but APTT tests are notoriously erroneous, and this result did not fulfill our criteria for the presence of lupus anticoagulant.

As the father was asymptomatic, there was no justification for further studies at this stage, and the question of whether he had a lupus anticoagulant remains academic. On the basis of an abnormal, though equivocal DRVVT result, and positive anticardiolipin antibodies, with his family history it is very likely that future samples would give unequivocally positive lupus anticoagulant tests, and development of suitable clinical criteria would classify him as a true antiphospholipid syndrome patient.

- 1 Thiagarajan P, Pengo T, Shapiro SS. The use of the dilute Russell viper venom time for the diagnosis of lupus anticoagulant. *Blood* 1986; 68:869-74.

NOTICES

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