



Figure 2 Calcified comedo-type ductal carcinoma in situ of breast in a thick section (1200 µm deep) stained with 0.0001% (w/v) alizarin red S (A), and a corresponding sliced specimen radiograph of the same tissue (B).

for staining other components of thick tissue sections.^{3,4}

Literal in-depth assessment of microcalcification and the changes in macromastia⁵ may also facilitate appropriate analysis of mammographic lesions and the diagnostic histological dilemmas resulting from reduction mammoplasty⁶ for macromastia.

S LEECH
J S ARMSTRONG
J KULKA
J D DAVIES

Regional Breast Pathology Unit,
Wolfson Foundation & Department of Pathology
& Microbiology, University of Bristol,
Bristol BS10 5NB

Prospective comparative study of computer programs used for management of warfarin

Poller *et al* refer to their experience with, among others, the Hillingdom system for computer-assisted warfarin maintenance.¹ Their numbers are small, and we should like to record our current experience with a larger series. Nearly all of our patients are given a target INR of 2.8. To compare these as nearly as possible with those of the above authors, who used a range of 2.0 to 3.0, we have used 2.3 to 3.3. The ranges used by these authors are narrow, and divergence from them does not necessarily mean that anticoagulation is at a level which is either ineffective or dangerous. We followed their division into the first 26 weeks of treatment and the period, if any, after that point. The results are shown in the table.

With the important exception of the interval between visits, our experience is not

- 1 Lane-Clayton JE, Starling EH. An experimental enquiry into factors which determine the growth and activity of the mammary glands. *Proc Roy Soc* 1904;505-22.
- 2 Marcum RG, Wellings SR. Subgross pathology of the human breast: methods and initial observations. *JNCI* 1969;42:115-21.
- 3 Armstrong JS, Davies JD, Hronkova B. Backprocessing paraffin wax blocks for subgross examination. *J Clin Pathol* 1992;45:1116-7.
- 4 Faverly D, Holland R, Burgers L. An original stereomicroscopic analysis of the mammary glandular tree. *Virchows Arch (Pathol Anat)* 1992;421:115-9.
- 5 Bässler R. Makromastie. In: *Pathologie der Brustdrüse*. Berlin: Springer-Verlag. 1978: 283-97.
- 6 Bondeson L, Linell F, Ringberg A. Breast reductions: what to do with all the tissue specimens? *Histopathology* 1985;9:281-5.

significantly different from that of Poller *et al* as shown in their table 4. Our mean intervals, both for early and later periods of treatment, are longer than theirs: this may be partly attributable to the maximum permissible interval having been increased from eight to 10 weeks during the period under consideration. We can add that the average interval at the latest visit was 7.04 weeks.

We have only six patients (187 visits) to compare with those who had a higher target INR. Having so few, we would only say tentatively that the average intervals before and after 26 weeks were 2.24 and 3.36 weeks, respectively, and that the interval at the latest visit averaged 3.83 weeks.

The mean interval is important, both for the convenience of patients and economy in the use of hospital resources. Our data support the inherently probable propositions that intervals become longer as treatment proceeds, and are much shorter with higher INR targets. Because they require more fre-

quent attendances, and also because they are more difficult to achieve, high targets require much justification on grounds of clinical necessity.

AH JAMES
RP BRITT

Department of Haematology,
The Hillingdom Hospital,
Uxbridge, Middlesex UB8 3NN

- 1 Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. *J Clin Pathol* 1993;46:299-300.

Vasculopathy and antiphospholipid antibodies in systemic lupus

We read with great interest the article by Ellison and colleagues showing intramural deposition of platelet derived material in small cerebral vessels in four patients with systemic lupus erythematosus (SLE).¹ The authors recall the strong association between the presence of antiphospholipid antibodies (aPL) and the occurrence of ischaemic cerebral events in SLE. The results of tests for aPL (lupus anticoagulant or anticardiolipin antibodies), however, are not mentioned in their patients with SLE. Such information could probably be obtained from the patients' charts or from stored serum or plasma. At least the full description of extra-neurological aPL related events—arterial or venous thrombosis, recurrent fetal loss, or thrombocytopenia—could suggest the presence of this peculiar family of antibodies. Such data could allow the hypothesis that intramural deposition of platelet derived material is a feature of a aPL-associated non-inflammatory "vasculopathy" to be tested. The absence of such material in the two patients with SLE and active vasculitis¹ is consistent with this hypothesis, due to the lack of an association between aPL and vasculitis in SLE.^{2,3}

Furthermore, the search for intramural deposition of platelet derived material should be performed in other forms of vascular lesions encountered in patients with antiphospholipid syndrome, either "primary" or secondary to SLE, such as non-inflammatory non-atheromatous large artery lesions^{2,3} and heart valve thickening,^{4,5} the latter being mainly present in patients with SLE, with long-lasting disease.⁴ The pathogenesis of these lesions remains unknown: it could involve a complex aPL mediated interaction between platelets and endothelial cells, resulting in platelet derived material incorporation into vessel or heart valve wall, which would explain the "mysterious" thickening frequently observed. Similar remarks could also apply to Sneddon's syndrome, a condition closely related to aPL,⁶ the pathological basis of which has been recently detailed,⁷ but the pathophysiology remains obscure.

JC PIETTE
C FRANCES
T PAPO
M KARMOCHKINE
Internal Medicine Unit,
Groupe Hospitalier Pitié-Salpêtrière,
75013 Paris France

- 1 Ellison D, Gatter K, Heryet A, Esiri M. Intramural platelet deposition in cerebral vasculopathy of systemic lupus erythematosus. *J Clin Pathol* 1993;46:37-40.
- 2 Lie JT. Vasculopathy in the antiphospholipid syndrome: thrombosis or vasculitis or both? *J Rheumatol* 1989;16:713-5.

	No of visits	% visits in range	% visits above range	% visits below range	Average interval (weeks)
Up to 26 weeks	2058	44.1	24.8	30.9	3.11
After 26 weeks	5332	50.5	24.8	24.6	5.81

361 patients; 7390 visits; target INR 2.8; range 2.3-3.3.

- 3 Piette JC, Frances C. Quelle est la nature des lésions vasculaires du syndrome des antiphospholipides? *Rev Med Interne* (in press).
- 4 Galve E, Candell-Riera J, Pigrau C, et al. Prevalence, morphologic types, and evolution of cardiac valvular disease in systemic lupus erythematosus. *N Engl J Med* 1988; 319:817-23.
- 5 Galve E, Ordi J, Barquinero J, et al. Valvular heart disease in the primary antiphospholipid syndrome. *Ann Int Med* 1992;116: 293-8.
- 6 Kalashnikova LA, Nasonov EL, Borisenko VV, et al. Sneddon's syndrome: cardiac pathology and antiphospholipid antibodies. *Clin Exp Rheumatol* 1991;9:357-61.
- 7 Zelger B, Sepp N, Schmid KW, et al. Life history of cutaneous vascular lesions in Sneddon's syndrome. *Hum Pathol* 1992;23: 668-75.
- 2 Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: Clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990;21:1168-80.

Relative friendly Death Certificates

I read Dr Slater's description of his audit of the wording of Death Certificates with interest,¹ and I agree that many of the inaccuracies he identifies are reprehensible. I take a far less hawkish view than he does about the commonest inaccuracy, however, which is to quote the mode of dying qualified by an underlying cause; an unqualified mode of death, on the other hand, is quite obviously silly. General practitioners may have to counsel a bereaved family when the only information they have about the death of their loved one is a Death Certificate, and I do not hesitate to include a mode of dying if I think that it will help with this counselling by clarifying the sequence of events. Why should "cardiac failure due to coronary atheroma" be deemed wrong when "myocardial infarction due to coronary atheroma" can be accepted? When I carry out a necropsy, I like to think that I can derive the greatest possible benefit for all concerned, including relatives, clinicians, and epidemiologists. I don't think the Office of Population Censuses and Surveys has any particular difficulty with a Death Certificate if I put in an extra line at the beginning which clarifies the mode of death, because it is the underlying cause of death which is selected.² Excluding modes of death from Death Certificates is one counsel of perfection which I shall happily ignore.

While on the subject of counsels of perfection, Dr Slater might like to know that the literature contains many references³⁻¹¹ about the poor correlation between the clinical and pathological diagnosis of terminal malignancy and necropsy findings. Most are much more informative than the one he cites.¹²

EW BENBOW

Department of Pathological Sciences
University of Manchester
Oxford Road
Manchester M13 9PT

- 1 Slater DN. Certifying the cause of death: an audit of wording inaccuracies. *J Clin Pathol* 1993;46:232-4.
- 2 Office of Population Censuses and Surveys. *1990 Mortality Statistics—Cause*. London: HMSO, 1991.
- 3 Gobatto F, Vecchiet F, Barbierato D, Melato M, Manconi R. Inaccuracy of death certificate diagnoses in malignancy: an analysis of 1,405 autopsied cases. *Hum Pathol* 1982;13: 1036-8.
- 4 McFarlane MJ, Feinstein AR, Wells CK, Chan CK. The "epidemiologic necropsy". Unexpected detections, demographic selections, and changing rates of lung cancer. *JAMA* 1987;258:331-8.
- 5 Anderson RE, Hill RB, Key CR. The sensitivity and specificity of clinical diagnostics during five decades. Toward an understanding of necessary fallibility. *JAMA* 1989;261: 1610-7.
- 6 Bloor MJ, Robertson C, Samphier ML. Occupational status variations in disagreements on the diagnosis of cause of death. *Hum Pathol* 1989;20:144-8.

- 7 Chan CK, Wells CK, McFarlane MJ, Feinstein AR. More lung cancer but better survival. Implication of secular trends in "necropsy surprise" rates. *Chest* 1989;96: 291-6.
- 8 Nemetz PN, Tangalos EG, Kurland LT. The autopsy and epidemiology—Olmsted County, Minnesota and Malmö, Sweden. *APMIS* 1990;98:765-85.
- 9 Di Furia L, Piga A, Marmili S, et al. The value of necropsy in oncology. *Eur J Cancer* 1991;27:559-61.
- 10 Papadakis MA, Mangione CM, Lee KK, Kristof M. Treatable abdominal pathologic conditions and unsuspected malignant neoplasms at autopsy in veterans who received mechanical ventilation. *JAMA* 1991;265: 885-7.
- 11 Hasle H, Mellegaard A. Hodgkin's disease diagnosed post mortem: a population based study. *Br J Cancer* 1993;67:185-9.
- 12 Slater D. "Patients with terminal cancer" who have neither terminal illness nor cancer. *Br Med J* 1987;295:669-70.

Dr Slater comments:

I appreciate Dr Benbow's interest in my audit of wording inaccuracies in relation to death certification. I fully support Dr Benbow's view that histopathologists should be "relative friendly". Locally, we attempt to achieve this by personal communication with general practitioners and, when appropriate, by spending time with relatives of the deceased. We find this is preferable to the necessary limitations imposed by attempting to glean information from a somewhat "stark" and impersonal Death Certificate. I agree that the inclusion of a "mode of dying" in expert hands (such as Dr Benbow's) does little harm. I am sure, however, that if such a policy was adopted by inexperienced doctors then mode of dying would quickly become acknowledged as a definitive cause of death. Perhaps we should also not forget that it is *cause* and not *mode* of death that we are certifying.

I am also appreciative of Dr Benbow's comprehensive list of references relating to the poor correlation between the clinical diagnosis of terminal malignancy and necropsy findings. This in itself proved an interesting audit and I was relieved that my own references were only 10% deficient. I was saddened to see that Dr Benbow expressed no personal opinion on the term carcinomatosis.

Further to Dr Slater's informative paper on audit of death certification we would like to add our experience in this field. Since 1990 we have audited the accuracy of death certification in this hospital by comparing the cause of death as found at post mortem (COD) with the presumed cause of death as written on the death certificate (PCOD). A post mortem examination is requested on all hospital deaths in this institution; the overall rate in three years is 24.2%, excluding coroners' cases, and thus the cases are not especially selected for post mortem examination. Accuracy of certification is scored 1-4: 1 = completely accurate; 2 = relatively accurate, the PCOD and COD match, but secondary causes are inaccurate or excluded; 3 = acceptably inaccurate where the PCOD may be mistaken for the COD, and 4 = completely inaccurate. The results are shown in the table.

Dr Ellison et al comment:

Dr Piette and colleagues make some valuable suggestions in their letter about our article. We were also keen to compare the presence of intramural platelet deposition and titres of antiphospholipid antibodies in our series of patients. Three of the six had died before antiphospholipid antibodies were regularly measured, however, and we could find no record of these tests in the case-notes of the other three. We were unable to trace any stored serum.

We would agree that a study of other vascular lesions in the antiphospholipid syndrome would be interesting. Though difficult to substantiate or to quantify, our impression was that intramural platelet deposition was more readily found in the cerebral vasculature of patients with the longest histories of neuropsychiatric symptoms and the most deformed, thickened, small vessels.

Carcinoid pattern in adrenal pheochromocytomas

In response to the paper by Harach and Bergholm,¹ I would like to comment on a similar phenomenon that I have encountered in two adrenal pheochromocytomas.

One case was sporadic and the other associated with multiple endocrine neoplasia type IIa (MEN IIa). The carcinoid areas seen microscopically were reminiscent of the classic midgut pattern with packets of uniform cells. The tumour cells were smaller and less pleomorphic than the typical pleomorphic, polygonal chief cells of the usual pheochromocytoma. These carcinoid foci were, however, minor histological components and both tumours had adjacent areas of typical pheochromocytoma. The medullary carcinoma of the patient with MEN IIa, interestingly, did not share this carcinoid phenotype. The question of metastatic midgut carcinoids was not entertained because of obvious areas of pheochromocytoma and the characteristic clinical scenario. At the same time, it must be remembered that metastatic medullary thyroid carcinoma within an adrenal pheochromocytoma has been described.²

Metastases aside, if one believes in the dispersed (diffuse) neuroendocrine system, it is not unexpected that overlaps in histological pattern will occur.

RUNJAN CHETTY

University of Oxford,
Nuffield Department of Pathology,
John Radcliffe Hospital,
Headington, Oxford OX3 9DU

- 1 Harach HR, Bergholm U. Medullary carcinoma of the thyroid with carcinoid-like features. *J Clin Pathol* 1993;46:113-7.

	Score				Total
	1	2	3	4	
1990	27 (28%)	43 (43%)	7 (7%)	22 (22%)	99
1991	23 (30%)	29 (38%)	9 (12%)	15 (20%)	76
1992	18 (29%)	27 (43%)	6 (10%)	11 (18%)	62