way, predispose to certain malignant neo-
plasms.1 Although these authors attempt to exclude external causes for suppression of
monocyte activity by comparing patients with
malignancy with other patients, this may not
be sufficient as a control. Monocyte esterase is
easily inhibited by several pharmacological and
environmental factors. Organophosphates,
used as a component in insecticides, are potent inhibitors of monocyte esterase.4
Monocyte esterase has been shown to be a
useful measure of occupational exposure to
organophosphates in plastics manufacturing.3
The excess in monocyte esterase deficiency
in patients with cancer observed by Markey et al
could be due to differences in drug exposure compared with patients who do not have cancer, or a tendency to report
familial studies in only 11 esterase negative
patients, of which five had cancer and six other conditions, out of a total of 90 esterase negative patients. Attributing esterase
deficiency to an underlying family trait is not
definitely known as the cause in most patients in their study. Their results are certainly important, however, and could lead to
future studies which might elucidate these
questions.

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Dr Markey comments:
The Haemolg D automated differential
white cell counter, producing as it did, a
monocyte count on esterase stained cells and a
monocyte count on peroxidase stained cells
(scores on each channel) was an excellent system for identifying monocyte
esterase deficiency. It is indeed unfortunate
that subsequent improvements to its technol-
ogy involved relinquishing the esterase channel.
The manual method of Ross et al, however, which involves the manual
staining for esterase of whole blood samples and counting the stained cells on the current Technicon H1 system, should permit confirma-
tion of previous studies. A peroxidase monocyte
score by the H1 must also be recorded for
each sample because a low esterase percentage
count can occur due to many other reasons.
A peroxidase monocyte count by the H1 will be
present on the esterase channel be accompa-
nied by a normal count on the peroxi-
dase channel.

We do not believe that the excess of esterase
deficient subjects among cancer patients can be
due to differences in drug exposure because
treatment regimens for different malignant
diseases are reasonably standard for the
treatment given in this hospital and radiotherapy centre, yet only a small propor-
tion of any malignant disease group manifes-
ted the anomaly. Moreover, of the group of
patients with carcinoma, six had not had any
chemotherapy or radiotherapy (primary diag-
nostic beds), while six had (oncology specialist
beds).Neither have we any evidence that our
subjects' deficiency was acquired as a result of
exposure to organophosphates. Levine et al (reported by Ross) did not
report any follow up of their esterase deficient
subjects after they had been removed from the
plastics production process, but one may
temperly expect recovery of monocyte esterase
activity developing monocytes when organophosphates disappear from the
blood stream, as occurred within 14 days of acute
organophosphate poisoning in the case reported
by Oehmichen et al.1 Fifty of our subjects
had confirmatory samples taken over 14 days
(mean 17 weeks) following the initial Haemolg D sample and many have had
repeat samples since then. None has reverted
to positivity. Moreover, we have no evidence of exposure to organophosphates, such as has
been reported by Levine et al. On the con-
trary, we have evidence of familial deficiency
in nine of 11 families studied (and in one
family of three studied in the interim period).
At this time we therefore feel that the balance
of our evidence is in favour of an inherent basis for the deficiency in our subjects.

As to our hypothesis that esterase deficiency may predispose to malignant neo-
plasms, we note that some studies have suggested that esterase deficient patients do not respond to
lactoferrin stimulation, with an increase in
cytotoxicity for K562 cells, using a modified
assay for measurement of monocyte cytotoxic-
ity; esterase positive monocytes respond vigorously (unpublished observations).

1 Oehmichen M, Pedal I, Besserer K, Gencic M. Inhibition of 
  monocytic leukemia esterase activity. Absence of monocyte
  esterase activity due to phosphoric and thiophosphoric acid
2 McCormick JA, Markey GM, Morris TC.
  Lactoferrin inducible monocyte cytotoxicity for K562 cells and
decay of natural killer lymphocyte (NK) cytotoxicity. Clin Exp
  Immunol (in press).

AgNORs and follicular lymphomas
It was of interest that Cronin and colleagues showed no significant difference between
AgNOR scores in follicular hyperplasia and follicular lymphoma.1 This confirms the results
of an original study in this laboratory some three years ago, where there was no numerical
difference in AgNOR score between
low grade lymphomas and hyperplastic
nodes. The slight trend to higher counts in
benign lesions, shown by Cronin et al,2 is to be
expected, as in most somatic tissues and
neoplasms, and certainly in non-Hodgkin's lymphomas, the interphase AgNOR score has
been shown repeatedly to be related to cell
proliferation.3 This latter is generally taken to
be greater in hyperplastic than malignant
(low grade) follicle centres. These observa-
tions would presumably only hold true if
follicle centre cells are enumerated; unfortunately,
this is not made clear by Cronin et al. AgNOR scores, however, can discriminate between
hyperplastic follicles and high grade
(pure centroblastic) follicles. I have examined
10 specimens of reactive follicular hyper-
plasia and 10 pure centroblastic follicular
lymphoma using the standard AgNOR sequence3
with 3 µm paraffin wax sections. The latter

had been shown to be of a B cell derivation by
means of standard immunophenotyping; eight were detected de novo, and two had
arisen by transformation from centroblastic-
centrocytic lymphomas. All AgNOR dots, both intra- and extra-nucleolar, were counted
in 200 follicle centre cells from each case. The
cells were selected at random from all levels of the follicle centres, excluding the mantle
zone. The range of values for reactive follicular hyperplasia was from 2.3 to 3.5
(mean 2.85; SD 0.43) AgNOR sites per nuclear
profile. In the centroblastic follicular
lymphoma specimens the range was from 4.8
to 10.1 (mean 6.12; SD 1.75) (figure). Thus
we have yet another example of a malignant
transformation carrying with it a higher mean
AgNOR score, doubtless as a result of the
proliferative overgrowth of neoplastic cen-
troblasts, which themselves have high mean
AgNOR counts.

1 Cronin K, Loftus BM, Dervan PA. Are
  AgNORs useful in distinguishing follicular
  hyperplasia from follicular lymphoma? J Clin
2 Cronker J, Nair PK. Nucleolar organiser regions
3 Cronker J. Nucleolar organiser regions. In:
  Underwood FCE, ed. Pathology of the nucleus.
  Heidelberg: Springer-Verlag, 91-147.

Dr Cronin et al comment:
We thank Dr Cronker for his interest in our
small study. Essentially we agree with his
comments. The point of our paper was that
although we did find a statistical difference
between the two groups studied (follicular
lymphoma and follicular hyperplasia) the
overlap was such that AgNOR counts had
no discriminant value as a diagnostic test in
the group of patients we examined. As
stated in our paper, we confined our study to
the centroblastic/centrocytic category of
follicular lymphomas; we evaluated cases
randomly within follicles, while omitting
identifiable macrophages. In our experience
(about 80-100 cases of malignant lymphomas
a year) pure centroblastic lymphoma is
relatively uncommon and so we chose to study centroblastic/centricytic follicular lymphoma. We accept Dr Crocker’s opinion that AgNOR counts may be useful in separating pure centroblastic lymphomas from reactive hyperplasia. We also agree that AgNOR counts reflect proliferative activity.¹

Pathologists’ ability to estimate percentage of luminal occlusion in coronary artery disease

I was most interested to read the letter from Drs Champ and Coghill.¹

In a small study, presented at the Pathological Society in London in January 1985,² we wished to answer three questions:

1. How accurate are pathologists in estimating the percentage of luminal occlusion in a coronary vessel?
2. What is the extent of variation among different pathologists estimating the same vessel?
3. Does the use of a diagram proforma help in the naked eye assessment of coronary artery disease?

Twenty-five segments of coronary artery taken at necropsy were selected to provide a range of concentric and eccentric stenoses. These were shown to 15 trainee and consultant pathologists whose experience ranged from two months to over 30 years. No prior warning was given to the participants and each in turn was asked to estimate the percentage area of the lumen which was completely occluded by intimal proliferation (percentage estimate) and to grade this subjectively into mild/moderate/severe stenosis (subjective estimate). Having done this, diagram performances (figure) were then produced and the pathologist was asked to repeat the exercise. When all the results had been recorded, luminal occlusion was determined by planimetric methods on elastic van Gieson stained sections using a Kontron Videoplan computer (objective measurement). Each of the 25 coronary segments was then assigned to one of the following groups: mild (0 to 30% occlusion), moderate (31 to 69% occlusion), or severe (70 to 100% occlusion) stenosis on the basis of the objective measurements.

We then compared the percentage estimates and the subjective (mild/moderate/severe stenosis) estimates that had been made without the diagrams and with the diagrams to the objective measurements. Not surprisingly, we found that the pathologists were most accurate in their estimations of coronary stenosis of less than 30% and greater than 70%.

The use of a diagram proforma improved the estimation of percentage of arterial occlusion, but the subjective estimate of arterial occlusion was not reproducible within this group of pathologists and was not improved by the use of the diagrams. This was because there was a wide range of values for luminal occlusion which different pathologists considered significant. Comparison of the percentage with the subjective estimates for each pathologist showed a range of 25% to 60% (mean 32%) occlusion for the lowest value in the moderate stenosis category. For the severe stenosis category, the lowest values ranged from 40% to 90% with mean 67% which compares with the degree of stenosis that is generally considered to be of clinical importance.³

We suggested that to improve accuracy and reproducibility among pathologists in the naked eye assessment of coronary artery stenosis:
1. Diagram proformas should be used as an aid to assessment.
2. One should always try to quote a percentage of luminal occlusion.
3. If subjective estimates are used, one should agree on the cut-off points for mild/moderate/severe stenosis.

Consequences of the provision of laboratory services of the National Health Service by commercial firms

I read this article by Shanks with great interest, and I would like to make some comments about it and about the general state of private pathology laboratories.

Many people may not know that J S Pathology is a public company quoted on the stock exchange and that Dr Shanks is the executive director. The laboratory is the largest in the United Kingdom and not attached to any medical or university department, and is about to move into purpose built premises in North London. The laboratory work is tailored to private medicine and has a low proportion of medical to non-medical staff, and the bulk of the work is biochemistry and haematology with some microbiology, rather a lot of cytology, and little histopathology.

Laboratories of this kind are almost invariably “demand led” whereby the tests are undertaken and interpreted by the clinicians who request them. With few pathologists available for advice, the consequences are that there is no control of the number and nature of the tests that are performed, in contrast to the NHS where pathologists are available for consultation concerning difficult clinical problems and will give advice on how the laboratory can help. Another result of the “tests on demand” approach is that aggressive drug companies will use these laboratories for promoting their products. The marketing of serum tumour markers is a good example of this.

With the advent of efficient cervical and breast screening programmes and the expansion of private medicine, the private sector must become responsible for its own organisation. The private sector should have the freedom to set its own direction and to make its own decisions.

Provision of laboratory services

Both Whitty et al and Shanks² seem to conclude that it is no longer feasible for small to medium sized pathology departments to function autonomously. I would agree with this point of view as it seems to be inappropriate for each district general hospital to attempt to provide a comprehensive on-site pathology service. Two questions then arise. First, which tests should be retained locally, and secondly, which laboratory should deal with those tests which are referred out.

In their conclusion Whitty et al seem to point one way forward. They propose a plan of action which is similar to the approach we have adopted.³ As part of our business planning we have completed a detailed review of our present working practices. We have now defined a number of pathology services which will be retained locally. The aim now is to refine the definition of these services by having detailed discussions with our hospital consultants and general practitioners.

The next step is then to determine how non-core pathology services should be provided. One option is to proceed with a process of competitive tendering for these services. Clearly, the result of this may be that tests are either referred to another district NHS laboratory or to a laboratory within the private sector. I favour the alternative option...
AgNORs and follicular lymphomas.

J Crocker

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