Responsibility for effective provision of the service includes all doctors. Who is not a manager?

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Bronchioloalveolar carcinoma

Bronchioloalveolar carcinoma accounts for less than 3% of all primary lung cancers but has attracted disproportionate interest because of its intriguing clinical behaviour and unusual pathological appearance. Indeed, pathologists have been so exercised by this tumour that some have given it 36 different names while others claim that it does not exist at all.¹

Tumour cells of many different origins may adopt a similar histological pattern in the distal airway, and the term bronchioloalveolar carcinoma is confined to those originating in bronchioles or alveoli; it excludes metastasising adenocarcinomas from the bronchus or distant sites.² The tumour may arise from ciliated, mucinous, or clara cells in the bronchiolar epithelium or from type II pneumocytes in the alveolus. The cells all grow as a single layer along the walls of the airspaces, and the unusual environment of the alveolus—with a plentiful supply of food, oxygen, water, and space—probably encourages many different cells to grow in the same way.

The cause of bronchioalveolar carcinoma is equally uncertain and interesting. Smoking and gender appear to be unimportant, while pre-existing lung damage—either local scarring or diffuse pulmonary fibrosis—is definitely associated. The strange case report of a man who developed the carcinoma after habitually going to bed with his mouth full of olive oil led to suggestions of a link with the inhalation of oil,³ although such a history is rare. The pathological similarity between bronchioloalveolar carcinoma and the viral disease of sheep jaagsiekte suggests an infectious cause, but epidemiological evidence does not support this hypothesis.

Clinically bronchioloalveolar carcinoma has two distinct forms.^{4,5} More common is an unremarkable peripheral lung tumour that may be diagnosed by needle biopsy: metastases are unusual, and five year survival after surgery is 70%. The second form is more distinctive and presents radiographically as consolidation affecting one or more separate lobes or segments. About 10% of these patients have bronchorrhoea, and spread is assumed to be airborne, although a multifocal origin cannot be ruled out. Regional and distant metastases occur less commonly than in other lung cancers, and death may therefore be from respiratory failure as more and more of the lung becomes occupied by the tumour. Because this type of bronchioloalveolar carcinoma is widespread surgery is ineffective, and neither radiotherapy nor chemotherapy help. Nevertheless, the tumour may grow slowly, and some patients live for three years after the

diagnosis. Both forms of the carcinoma (as well as the metastatic adenocarcinoma) may progress to widespread pulmonary nodules, and at this stage it is uncertain whether spread occurs by blood or airways.

Recently attempts have been made to classify bronchioloalveolar carcinoma cytologically into mucinous (secretory), non-mucinous (non-secretory), and undifferentiated groups.^{6,7} The mucinous variety tends to associate with multifocal disease, and the non-mucinous with peripheral nodules, while distant metastases are more common in the undifferentiated group; but these correlations are imprecise. Since bronchioloalveolar carcinoma represents many tumours with similar histological appearance clinicopathological correlations will remain difficult until the cell of origin can be identified more reliably.

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Haematology, ethnography, and thrombosis

The activities of the coagulation and fibrinolytic systems and the reactivity of platelets vary as widely as the haematological indices measured by a "full blood count." Such differences are of interest to those who wish to understand thrombosis: if those at high risk of thrombosis could be identified by examining factors that promote or control fibrin and platelet deposition steps might be taken to prevent the thrombosis.

Identifying relations between blood values and thrombosis has not proved easy. In certain individuals thrombosis is linked to a congenital deficiency of certain blood factors—for example, antithrombin III, protein C, or plasminogen activator—but such deficiency states are rare and in most people the reason for a thrombosis is unknown. The main reason for our slowness in getting to grips with the problem may be that blood values change dramatically after a thrombosis.

The prospective approach is most likely to yield information, and several studies of patients at high risk of venous thromboembolism—for example, surgical patients—have suggested a relation between haematological values and thrombosis. For example, evidence of "hypercoagulability" (short activated partial thromboplastin time, higher factor VIII activity, higher concentrations of fibrinogen and fibrin degradation products, and prolonged euglobin lysis time) was found preoperatively in plasma from surgical patients who went on to develop venous thromboembolism.¹²

The information that we have for arterial thrombosis is derived from a few very large studies in which haematological

(and other) indices were measured in several hundred people and then subsequent coronary or cerebrovascular events recorded. In the Northwick Park Heart Study of 1511 white men aged 40 to 64 at recruitment both high factor VII activity and high plasma fibrinogen concentrations were strongly associated with ischaemic heart disease.^{3,4} In both cases the association was particularly strong for the subgroup of men who developed heart disease within five years of their blood being examined. The findings are intriguing in that the associations with coagulation factors seem stronger than that between cholesterol concentrations and heart disease. Fibrinogen concentration has also been identified as a risk marker in a smaller prospective study of coronary disease⁵ and in a prospective study of myocardial infarction and stroke.⁶ In other investigations a high white cell count has also proved to be a risk marker for myocardial infarction and stroke.^{7,8}

In general the incidence of thrombotic disease in black people is lower than that in whites, and findings that blood from healthy whites is "hypercoagulable" or displays a lower fibrinolytic activity, or both, when compared with blood from healthy blacks^{9,10} support the concept that blood composition may contribute to developing thrombosis. Until recently, reports of coagulation and fibrinolytic studies in different ethnic groups have been limited to subjects in one geographic locality because haematological indices can be compared only if methods are standardised. Standardisation is often difficult between adjacent laboratories, never mind countries, but, using continuous external quality control of the laboratory measurements, the World Health Organisation has started a study to compare the effects of different oral contraceptives on coagulation, fibrinolysis, and platelet "function" in women from diverse geographical locations. A recent article records the baseline data from clinical centres in Dublin, Salvador (Brazil), Santiago (Chile), and Singapore.¹¹ The women in the study are to be given oral contraceptives, which makes the decision to study these particular centres surprising given the Catholic influence in some of them, and women recruited in, for example, Dublin are unlikely to be a completely random sample.

Data were provided for just under 200 women at each centre. Not all of it stood up to the external quality control, but the information was sufficient for some clear patterns to emerge. The most interesting data came from Dublin (where all the women were white) and from Salvador (where the women were predominantly black or mulatto). Blood from the Dublin women turned out to be "hypercoagulable" (short prothrombin time, short activated partial thromboplastin time, increased factor X activity, and increased concentration of antipiasmin) while that from the Salvador women turned out to be "hypocoagulable" (prolonged prothrombin time, prolonged activated partial thromboplastin time, lower factor VII activity, increased plasminogen activator activity, and decreased concentrations of antipiasmin). In contrast, the Dublin women had higher concentrations of antifactor Xa and antithrombin III (which may, the authors suggest, protect against the hypercoagulability), and the Salvador women had lower concentrations of these antiproteases. Unfortunately information on white cell counts was incomplete and the platelet studies were not fully standardised.

The authors of the report consider the data in terms of "the clinical impression that the 'epidemic' of thromboembolism... in Western countries has not been shared by the developing parts of the globe where clinical evidence of thromboembolism is relatively rare." A critical study of

venous thrombosis in Nigerians questioned, however, the previous largely clinical impression of a lower incidence of the disease in this population.¹² The WHO investigators must now copy Meade *et al*¹¹ and follow up the patients to determine the actual rates of thrombosis. Some information may be obtained as a byproduct of giving oral contraceptives—provided that the group studied is large enough and the procedures adopted to detect thrombosis well standardised.

Prospective and large scale comparative studies (particularly in diverse geographical locations) are expensive and require much organisation and energy, huge resources, and good quality control. Nevertheless, this type of study will tell us most about the aetiology of thrombosis—information of fundamental importance if the disease is to be controlled.

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Coffee, cholesterol, and colon cancer: is there a link?

Drinking coffee may raise serum cholesterol concentrations. The association was first observed by Bjelke in Norway in 1974¹ and has since been confirmed in three much larger Norwegian studies, one of which has been published in detail.² The association has also been observed in some, but not all, studies from other countries.³⁻⁷ That coffee (at least coffee brewed in the north Norwegian way) may actually cause the rise in cholesterol concentration has been suggested by two small experiments.^{8,9}

Coffee drinking may also be associated with a reduced risk of developing cancer of the colon. Bjelke found this to be so in his case-control studies with 162 cases in Norway and 259 cases in Minnesota,¹⁰ and similar findings have been reported from two other case-control studies.^{11,12} But no association was seen in two other case-control studies,^{13,14} and in a third "a significant but small excess risk" of colon cancer was associated with high coffee consumption.¹⁵

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