myalgia arteritica do abate spontaneously and completely within two years of onset, most do not: the disorder tends to return if the dosage is dropped too soon below the critical level. All too often treatment is stopped prematurely before the disease has burnt out; not only may relapse occur on reductions as small as 0.5 mg of prednisone daily, but after steroid treatment has been stopped the disease may apparently light up again some weeks or even months later. Nevertheless, given the right drug in the correct dosage for the right period of time, few conditions in medicine are more amenable to treatment, and few patients are more grateful to their doctor for the rapid and lasting relief than those with this strange disease.

1 Horton, B T, Magath, T B, and Brown, G E, Proceedings of the Staff Meetings of the Mayo Clinic, 1932, 7, 700.
4 Bagratuni, L, Annals of the Rheumatic Diseases, 1953, 12, 98.
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ACTH-secreting lung tumours

Inappropriate hormone secretion occurs in many malignant tumours, and ectopic corticotrophin (ACTH) production is one of its more common varieties. Most ACTH-secreting tumours arise from the lung, almost exclusively oat-cell carcinomas and bronchial carcinoids. Some patients develop the florid clinical manifestations of Cushing’s syndrome with hypokalaemic alkalosis, but usually there are no obvious signs and the condition is recognised by biochemical assays of plasma concentrations of cortisol and ACTH.

Bloomfield and his colleagues have recently measured the concentrations of ACTH in 14 lung tumours selected at random but not associated with the ectopic ACTH syndrome. The tumours were removed by pneumonectomy or lobectomy or by local excision in the case of carcinoid tumours. At the same time lung tissue at a distance from the tumour and macroscopically free from it was used as a control. All the examples of oat-cell carcinoma and carcinoid tumour contained substantial amounts of ACTH, as did also an adenocarcinoma with large-cell carcinoid elements. By contrast, the squamous-cell, anaplastic, and glandular tumours contained insignificant amounts of ACTH, the only exception being a poorly differentiated squamous-cell carcinoma which may possibly also have contained carcinoid elements.

Of even greater interest was the finding of ACTH in the non-tumorous lung tissue, correlating well with the tumour concentrations. This could not be attributed to contamination by sequestered blood, since there was no significant correlation between ACTH concentrations in the plasma and the lung tissue, and the latter was taken at a site as remote from the tumour as possible. Bloomfield et al suggested that ACTH was being produced in widely dispersed cells in the lung, either as a premalignant change or secondary to tumour formation in a field of growth that included the whole lung. Alternatively, the hormone-secreting granules might themselves have metastasised and become incorporated into other parts of the lung tissue.

Just how frequent ectopic hormone secretion is in malignant tumours is only now becoming clear. Probably all oat-cell carcinomas and carcinoid tumours of the lung synthesise ACTH-like materials, though clinical evidence of the ectopic ACTH syndrome is usually absent. Presumably it is the level of secretion that determines whether clinical effects occur or not. If there were a greater correlation between tumour and plasma concentrations of ACTH it might be possible to diagnose these tumours biochemically or to detect an early recurrence after removal. But at present the observation is more of pathological interest than clinical importance.


Anticoagulants and heart valve replacement in pregnancy

More and more women of childbearing years have undergone heart valve replacement. The indications have been various: congenital, postinfective, or rheumatic heart disease (which is still as common as ever in many parts of the world). Patients given a prosthetic valve are generally believed to require lifelong anticoagulants to reduce the incidence of thromboembolic complications. Though the risks of thromboembolism are appreciable with the older types of heart valve prostheses, experience with the Starr-Edwards and homograft valves has shown that these reduce the incidence of such complications. Furthermore, the risks associated with replacing the aortic valve alone are much less than with mitral valve prostheses. From a recent questionnaire survey of current practice among cardiologists in the United Kingdom Oakley and Doherty concluded that anticoagulants are mandatory in patients with mitral valve prostheses, but that the indications appear less strong after tissue valve replacement, particularly of the aortic valve.

Problems inevitably arise in continuing anticoagulant prophylaxis during pregnancy, for, while the treatment may be safe and effective for the mother, there may be hazards to the fetus. During pregnancy the concentrations of some blood clotting factors are increased while the protective influence of the blood fibrinolytic mechanism is reduced. These changes promote good haemostasis at delivery, but they may produce an increased tendency to thromboembolism. Any decision to withdraw long-term anticoagulant prophylaxis is complicated by clinical evidence of an increased risk of embolism when anticoagulants are stopped in pregnancy, particularly during the withdrawal period, presumably owing to rebound hypercoagulability.

Hazards to the fetus result from the passage of coumarin-type drugs through the placental barrier; fetal haemorrhage may occur, partly due to immaturity of the fetal liver. Coumarins also have teratogenic effects. Abortion, stillbirth, congenital abnormality, and perinatal morbidity are all thought to be increased by use of oral anticoagulants, and the fetal mortality from anticoagulants during pregnancy has been put as high as 15%.

Subcutaneous heparin appears to be a much safer way of anticoagulation during pregnancy, though the need for twice-daily injections throughout is somewhat daunting. But, though inconvenient to administer, heparin has the great
advantage of not being passed through the placental barrier. Its use may also avoid haemorrhage associated with birth trauma, since the blood level returns to normal quickly after simple withdrawal of the drug when labour begins.

The best compromise, based on the regimen recommended by Bonnar,\(^6\) is as follows. Heparin should be given subcutaneously during the first trimester, to avoid any risk of teratogenic effects from oral anticoagulants. Between 12 and 37 weeks oral anticoagulation may be re instituted. The risk of fetal haemorrhage during this period may be minimised by using a relatively conservative dosage regimen.\(^7\)\(^8\) The aim should be to prolong the prothrombin time ratio to 2·0 to 2·5 using the Quick test with the British (Manchester) thromboplastin reagent. At 37 weeks the subcutaneous heparin regimen should be restarted. For safe and effective treatment, plasma heparin concentrations should be monitored, especially in the last trimester, because during pregnancy women become relatively refractory to its anticoagulant effect. Between 7000 and 10 000 units of heparin are normally required 12-hourly to provide the optimum concentration of 0·1 to 0·4 units per ml. This may be controlled by assay\(^9\) of antiactivated factor X or the standardised partial thromboplastin time test.\(^10\) Forty-eight hours after delivery oral anticoagulants may be started again, with vitamin K supplements to the baby if breast-fed.

Further work is required to establish the relative value of alternative regimens such as continuous heparin throughout pregnancy, with or without the addition of antiplatelet drugs such as dipyridamole. Meanwhile, most patients with heart valve prostheses who need anticoagulant prophylaxis can undergo pregnancy without much trouble to the mother—while the risks of oral anticoagulants to the fetus can be minimised.

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**Cytomegalovirus in immune compromised hosts**

Wider use of cancer chemotherapy has led to the recognition of its less usual infective complications. These may be puzzling. An infecting bacterial organism can be identified in only 10\% or so of patients who develop sustained fever while on chemotherapy for induction of a remission of acute leukaemia. Viral infections are assumed but rarely proved. Nevertheless, infection with cytomegalovirus (CMV) can be identified by histological, serological, and virological methods in as many as 90\% of patients who have had renal transplants and are on drug treatment to prevent the rejection of the donor kidney.\(^1\)

In these patients infection has been attributed to the immunosuppressive effects of treatment, though the extent to which chemotherapy is immunosuppressive is arguable. The bone marrow suppression which follows chemotherapy undoubtedly increases susceptibility to infection, but granulocytopenia alone does not appear to predispose to infection with CMV. Therapeutic doses of immunosuppressive drugs do not seem to alter antibody responsiveness, nor do circulating antibodies to CMV have much effect on the clinical consequences of infection. This is not entirely surprising: CMV is predominantly an intracellular virus transmitted by cell-to-cell contact and is therefore likely to be little affected by antibody. Nevertheless, intensive chemotherapy does reduce the circulating population of T lymphocytes,\(^2\) suggesting a quantitative impairment of cell-mediated immune responsiveness. This finding and the clinical consequences of chemotherapy support the case for cell mediated immunity being the controlling factor in infections with CMV. Further evidence has come recently from a study\(^3\) of 131 patients with rheumatological disorders and 211 unselected blood donors; CMV was isolated from the urine of 20\%, of the patients on cytotoxic immunosuppressive drugs but not from any of the patients on other forms of treatment.

Circulating complement fixing antibodies to CMV provide evidence of past exposure to the virus, and serological studies suggest that apparent infection with CMV often occurs early in life. The incidence of antibodies rises steadily with age to a plateau around the 40s. During active infection there is a rapid rise in antibody titres to CMV and the virus may be excreted in the saliva and urine for a long time afterwards. In Dowling's study\(^4\) 8 out of 14 patients who were given immunosuppressive therapy developed evidence of CMV infection. Seven of these eight patients had pre-existing CMV antibody, suggesting that immunosuppression might have reactivated endogenous infection.

The clinical features of CMV infection may resemble the Paul-Bunnell negative syndrome of infectious mononucleosis that may follow massive fresh blood transfusion; there may be prolonged fever, jaundice, ulceration of the gastrointestinal tract, arthralgia, retinitis, and skin eruptions. CMV may also cause an interstitial pneumonitis, which may progress to cause respiratory failure and death.\(^4\) Of 16 patients proved to have CMV by lung aspiration or biopsy, 13 had radiographic evidence of diffuse interstitial or alveolar infiltrates. Respiratory symptoms varied in duration from a relatively rapid course of one week to as long as seven weeks. Only one of these patients had evidence of acute hepatitis, and no patient had atypical lymphocytes on peripheral blood smears. Complement fixing tests for CMV were positive in only seven out of 12 patients investigated, indicating that serological tests alone may not necessarily help in the diagnosis of pulmonary CMV infection in patients with underlying disease. Another recent study looked at patients given bone marrow transplantation: interstitial pneumonia was the single most troublesome infectious complication.\(^5\) About half the patients with interstitial pneumonia had unambiguous evidence of disseminated CMV—characteristic inclusion bodies on histological examination of the lungs and other organs as well as isolation in culture. Retrospective analysis of virological and histological data suggested that at least one-third of patients undergoing bone marrow transplantation contract or activate latent cytomegalovirus infection during the first few months of engraftment. Patients with considerable rises in complement fixing antibody titre either have no clinical manifestation or have recovered from transient interstitial pneumonia, and most excrete cytomegalovirus in the urine. In contrast, those who develop fatal cytomegalovirus pneumonia (proved at necropsy) rarely have

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