linked immunosorbent assay (ELISA) using antibody class capture.⁶ This procedure is now available in British reference laboratories and is more sensitive and specific than the hitherto widely used IgM immunofluorescent antibody test (IFAT).³ Single high titres of IgG antibody measured by the Sabin Feldman dye test and haemagglutination tests are rarely useful in identifying recent infections; theoretically rising titres are helpful but, in practice, because of timing of samples, rarely are so.² A rapid, highly sensitive, and specific latex agglutination screening test is becoming increasingly available in general microbiological laboratories in order to detect IgG antibody in sera. Specimens giving a positive result may then be forwarded to the reference laboratories for full investigation.⁷ New methods of differentiating acute disease from chronic infection by detecting parasite antigens are being developed.^{8,9}

Postnatally acquired clinical toxoplasmosis usually presents as an illness like glandular fever but in some patients the lymphadenopathy may be an isolated finding, unaccompanied by fever, and sometimes associated with lethargy and malaise. Such patients are likely to be investigated by biopsy of a lymph node as well as or instead of with microbiological tests—because of concern about neoplastic or granulomatous disease. The cellular changes of acute glandular toxoplasmosis are characteristic^{4,10-13} but not necessarily diagnostic, and probably histological diagnosis should always be supplemented by isolation studies or serology or both.¹¹

Two recently published studies have confirmed earlier work showing that the cytopathological features of acute glandular toxoplasmosis closely parallel the histopathological changes, thereby adding fine needle aspiration biopsy to the diagnostic armament.¹⁴⁻¹⁶ A toxoplasma cyst was identified in material from one patient.¹⁵ Although all patients in whom it was measured had high concentrations of specific IgM (IFAT), the usefulness of cytological tests in diagnosing recent infection was compared not with this serological investigation but, inexplicably, with that of the dye test titre.

In Britain the number of cases of lymphoglandular toxoplasmosis diagnosed by biopsy alone is unknown. Only 5% of such cases diagnosed serologically are reported to have the diagnosis confirmed histologically.¹⁷ Clearly the approach to the patient with unexplained lymphadenopathy should depend on the diagnostic probabilities suggested by the history and clinical examination. The possibility of a dual diagnosis of both lymphoma and toxoplasmosis has also to be considered.⁴ Many clinicians choose open biopsy to examine the architecture of the lymph nodes, although others will prefer needle biopsy, which will be appropriate in certain patients. Yet recent toxoplasmosis is still probably best diagnosed by serology—which is in any case necessary to confirm the histological findings.

The fear advanced in the United States that young adults with unexplained lymphadenopathy will need to be protected from “enthusiastic surgeons” because of this latest advance in the diagnosis of toxoplasmosis seems unlikely to be realised in Britain.¹⁸ Like many non-infectious diseases, toxoplasmosis is in danger of becoming another diagnosis made by a multitest process. A combination of clinical judgment and a close working relationship between the clinician and the laboratory should, however, still be able to spare the patient from too many investigations.

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Treatment of advanced carcinoma of the prostate

About 6000 new patients will be found to have carcinoma of the prostate in Britain in 1984. Most of these will have metastatic disease at the time of presentation. In a consecutive series of 100 patients 32% of those with early tumours and 61% of those with advanced local disease had bony metastases.¹ Lymph node metastases are far more common than was previously thought and occur in up to 60% of patients without evidence of bony metastases.² And the outlook is poor: in a collected series only 6% of untreated patients with metastatic disease survived five years.³

Effective endocrine treatment for prostatic cancer became available in 1941 after the reports by Huggins and Hodges.⁴ The initial euphoria was soon tempered. Blanchot and Laporte drew attention to the cardiovascular complications associated with oestrogens,⁵ and oestrogen related problems were borne out by large prospective trials in the United States.⁶ These studies showed that the mortality and morbidity associated with treatment with oestrogens were unacceptably high.⁷ It was apparent that the individual risk for cardiovascular side effects induced by oestrogens is enhanced in those with a previous disposition—for example, the elderly and those who have undergone recent surgery.⁸

Stilboestrol in a dose of 1 mg three times a day appears to be as effective for treatment as higher doses, with correspondingly less (but still substantial) cardiovascular effects. Orchidectomy is used by some urologists as an alternative to oestrogens because cardiovascular problems do not occur, but it is unacceptable to many patients—and their urologists. Impotence and gynaecomastia are common with both treatments. A combination of orchidectomy and stilboestrol has been shown to be the best treatment for those with metastases at the time of presentation, though neither treatment has been convincingly shown to improve survival.⁹ One fifth of patients will not respond to this form of treatment, though it may be possible to predict those who will by measuring the nuclear androgen receptor content of the tumour.¹⁰ Of the responders, over half will relapse within two or three years, and this reactivated form of the disease is usually hormone resistant.

In short, refinements in conventional treatment are un-

likely to produce any major improvement in prognosis. New approaches are clearly needed, and superactive analogues of gonadotrophin releasing hormone have recently been introduced. These analogues cause initial pituitary stimulation, resulting in a rise of both luteinising hormone and testosterone, but by three weeks considerable down regulation occurs and concentrations of testosterone are lowered to castrate levels.¹¹ In the initial reports 42 of 52 patients responded.¹²⁻¹⁶

In a longer term study, however, four of 16 patients showed progression of their disease within one year. In 11 patients for whom data are available the serum concentration of luteinising hormone rose substantially over the 24 hours after each daily injection of the analogue, the amount of the rise increasing with the duration of treatment. Three of these patients also showed rises in testosterone concentrations—and progression of their disease.¹⁷ The mechanism of this failure to maintain a down regulation of the luteinising hormone releasing hormone receptor has considerable implications for the use of peptide analogues. It may result from an alteration of the receptor which no longer accepts the analogue or an "up regulation" by the receptors. An alternative may be the formation of antibodies against the peptide analogue. Luteinising hormone releasing hormone analogues have not been shown to produce any objective evidence of disease remission in patients who have relapsed or failed to respond to conventional endocrine treatment, though most experienced some short term relief of pain.¹⁸ Depot preparations of the analogue given subcutaneously every 28 days are now under study.

High doses of ketoconazole, an antifungal agent in common use, drastically but reversibly reduce serum concentrations of testosterone in men to values around the castrate range, and they also block production of adrenal androgens.¹⁹ An initial report of the use of ketoconazole as a primary treatment in patients with advanced prostatic cancer is encouraging, though not all the patients reached or maintained castrate levels of testosterone and a strict eight hourly dose regimen is essential.²⁰ It is unlikely that any single treatment aimed at reducing serum concentrations of testosterone will produce any substantial benefit compared with orchidectomy. The combination of a luteinising hormone releasing hormone analogue with ketoconazole—blocking production of androgens by both the testes and the adrenals—should, however, be worthy of much further study. Allen *et al* have reported on two patients treated with ketoconazole who had relapsed after both conventional treatment and treatment with luteinising hormone releasing hormone.²¹ Both patients showed a fall in acid phosphatase. A further 17 patients who were unresponsive to hormones and luteinising hormone releasing hormone have been treated. Seven have shown reductions in acid phosphatase and six have shown objective improvement, using nuclear magnetic resonance scans for local disease and radionuclide bone scans for metastases. Further falls in the already castrate concentrations of testosterone, dihydrotestosterone, and androstenedione without any alteration of plasma cortisol concentrations were seen in

those patients who were able to take high dose ketoconazole, 1200 mg daily.¹⁹

These new approaches to the treatment of prostatic cancer open up an exciting range of therapeutic possibilities. Labrie *et al* have reported successful treatment of prostatic cancer using a luteinising hormone releasing hormone analogue in combination with an antiandrogen to block both the initial rise in testosterone production and the action of residual testosterone after the medical castration.²² Studies are urgently required to evaluate the combination of luteinising hormone releasing hormone or orchidectomy with ketoconazole or dexamethasone or both to block adrenal androgen synthesis.

Treatment with hormones for prostatic cancer has never been convincingly shown to improve patients' survival, but such treatment did not take into account the contribution of the adrenal glands to the production of androgens or the need to block the action of residual androgens. Drugs are now available to achieve these ends. Further study is needed of combination treatment designed to suppress the production of androgens virtually completely.

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