Comment

Although it is easy to understand how this neuropathy may be missed, it is important to recognise it, for if it passes unnoticed patients may be accused of having given up or are thought to be deteriorating and so less vigorous treatment may be instigated. Even in patients with complete paralysis recovery may be remarkable.³ A neurological assessment will pick up most cases, but as this may be difficult electrophysiological confirmation of the neuropathy is advisable. Recognising the neuropathy (and the myositis and encephalopathy also seen in this patient) of severe illness is the first step towards finding an explanation; currently the aetiology is obscure because many metabolic, toxic, nutritional, and septic factors may be implicated. The condition to which it is most closely associated is shock lung.²

We thank Mr Malcolm Simms for referring the patient and Dr M P Carey for the interpretation of the muscle and nerve pathology.

ADDENDUM—We have recently seen another case of neuropathy in a critically ill patient. The primary disease in this case was uncertain, although the patient had pancreatitis and adult respiratory distress syndrome in conjunction with hepatorenal failure.

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(Accepted 13 June 1986)

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Serum concentrations of sex hormone binding globulin in lung cancer

The presence of low circulating total androgen concentrations in patients with lung cancer and of sex steroid metabolising enzymes and receptors in lung tumour tissue is well documented.^{1,2} No previous study, however, has measured sex hormone binding globulin concentrations, which would allow the physiologically active fractions of sex hormones free from binding to sex hormone binding globulin and albumin to be calculated. We measured sex hormone binding globulin concentrations and circulating concentrations of testosterone, 5 α -dihydrotestosterone and 17 β -oestradiol in 13 men with lung cancer and two control groups matched for age.

Patients, methods, and results

We studied three groups of volunteers—namely, 13 men aged 45-76 (mean 55) with histologically confirmed carcinoma of the lung (squamous (five), adenocarcinoma (four), undifferentiated (four)), of whom nine had disseminated disease; 14 men aged 49-75 (mean 59) with primary malignancies of other sites (cholangiocarcinoma (four) and carcinoma of the colon (four), stomach (three), and urinary bladder (three)), of whom 10 had disseminated disease; and 20 healthy controls aged 45-75 (mean 57). Disability as assessed by the Karnofsky score was 50-80% in both groups of patients with tumours. No patient was receiving any treatment known to affect circulating sex steroid concentrations or had received radiotherapy or cytotoxic chemotherapy. Gynaecomastia and hypogonadism were not noted in any of the patients with tumours. Analysis of sex hormones was by radioimmunoassay, and assay of sex hormone binding globulin was by the method of Iqbal and Johnson.³ The free fractions of the hormones were calculated by an interpolation method based on experimental data.⁴ Statistical analysis was by the Mann-Whitney U and Student's *t* tests.

All of the patients with cancer had low total androgen concentrations ($p < 0.02$) (median testosterone concentration 3.9 nmol/l (113 ng/100 ml) in the patients with lung cancer and 7.0 nmol/l (202 ng/100 mg) in those with other malignancies) and normal oestrogen concentrations (median oestradiol concentrations 135

pmol/l (3.7 ng/100 ml) in the patients with lung cancer) compared with the healthy controls (median testosterone concentration 14.5 nmol/l (418 ng/100 ml), oestradiol concentration 159 pmol/l (4.3 ng/100 ml)). Sex hormone binding globulin concentrations were also raised in all patients with cancer (figure), although those in the patients with lung cancer (up to 10 times normal) were significantly higher ($p < 0.002$) than those in the patients with other malignancies. Because of the high affinity of sex hormone binding globulin for androgens the patients with lung cancer had extremely low free androgen concentrations (median free testosterone concentration 15 pmol/l (0.4 ng/100 ml)), which were significantly lower ($p < 0.02$) than those in the patients with other malignancies (29 pmol/l (0.8 ng/100 ml)); the concentration in the healthy controls was 790 pmol/l (23 ng/100 ml). The usual negative correlation between sex hormone binding globulin and total 5 α -dihydrotestosterone concentrations observed in the healthy controls and the patients with other malignancies was reversed in the patients with lung cancer (correlation coefficient 0.65, $p < 0.01$).

Sex hormone binding globulin concentrations (expressed as nmol dihydrotestosterone (DHT) bound/l serum) in the three study groups. — = Median value; --- = mean value.

* $p < 0.002$ compared with healthy controls. † $p < 0.002$ compared with patients with other primary tumours.

Comment

Low total serum androgen concentrations, together with moderate increases in sex hormone binding globulin concentrations, have been observed in many patients with primary malignancies at various sites.⁵ Extremely high concentrations of sex hormone binding globulin leading to extremely low free androgen concentrations have not been reported before in men with lung cancer. Normal total oestradiol concentrations in these patients together with the lower affinity of oestrogens for sex hormone binding globulin result in a profound alteration in the balance of sex steroids towards the oestrogens. We were unable to distinguish any difference in sex steroid or binding globulin concentrations between patients with lung tumours of different histological types, but a larger study might show such differences. The causes of this increase in sex hormone binding globulin concentration in patients with lung cancer are not clear. Normally sex hormone binding globulin concentrations are inversely correlated with total 5 α -dihydrotestosterone concentrations, whereas in these patients a positive correlation was observed, suggesting that the normal homeostatic mechanisms controlling circulating binding globulin concentrations were no longer operational.

We thank Dr J Costello and the staff of the chest unit at this hospital for their help with this study.

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(Accepted 3 July 1986)

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Effect of passive exposure to smoking on age at natural menopause

Several studies have shown that women who smoke cigarettes reach the menopause sooner than those who do not, irrespective of potential confounding factors including marital state, parity, and body weight.¹ The reason for this is unknown, but it may be due to the destruction of irreplaceable primary oocytes by benzo(a)pyrene and other toxic substances in cigarette smoke.² Because exposure to toxic agents in tobacco smoke may also occur from passive smoking (including transplacental exposure³ and inhalation of ambient tobacco smoke) we investigated associations between passive exposure to smoking and age at natural menopause.

Subjects, methods, and results

We studied 261 women aged 35 and over who had acted as controls in a previous case-control study.⁴ Data were analysed with the Kaplan-Meier procedure and conditional logistic regression⁵ by methods analogous to life table analysis of survival data in a clinical trial or cohort study. In the life tables "survival" was equated with remaining premenopausal, "death" with the onset of menopause, and "withdrawal" with being interviewed before menopause or reporting a non-natural menopause.

The Kaplan-Meier estimate of mean age at natural menopause was 49.7 years for smokers and 50.8 years for non-smokers. The mean ages in non-smokers whose spouses also did not smoke and non-smokers whose spouses smoked were 51.9 and 49.8 years respectively (figure).

In a model comparing active smokers with non-smokers by conditional logistic regression only a modest increase in the risk of early menopause (odds ratio (OR) 1.3; approximate 95% confidence interval (CI) 0.8 to 2.2) was shown. Much stronger trends were evident when subjects who reported no exposure to active or passive smoking were compared with subjects exposed to either only passive smoking (OR 1.9; CI 1.0 to 3.9) or to active smoking (OR 1.9; CI 0.9 to 3.7). Race, education, year of birth, and alcohol intake were not significant independent indicators of the risk of early menopause; including them as covariates increased the estimates of risk associated with both active (OR 2.3; CI 1.1 to 4.9) and passive (OR 2.1; CI 1.0 to 4.5) smoking. Early exposure of a woman to smoking by her father was not associated with a risk of early natural menopause (OR 1.1; CI 0.6 to 1.9). The mean age at menopause was 2.2 years younger among women whose mothers smoked, but only four subjects were in this group.

Comment

In previous studies of the association between exposure to smoking and age at menopause non-smokers included subjects who might have been passively exposed to smoking. Our study, though much smaller, refined the

classification of subjects by omitting passive smokers from the group of non-smokers. This reclassification increased the difference in ages at menopause from 1.1 to 2.2 years and increased estimates of the risk of early menopause associated with active smoking in our data from 1.3 to 1.9. These differences show the importance of distinguishing non-smokers who are passively exposed from those who are not.

Our data also suggest that early natural menopause is associated with passive smoking. The increase in risk of early menopause observed for passive smoking was of similar magnitude to that observed for active smoking, but the study population was small and the true magnitude of

Kaplan-Meier estimates of cumulative proportion of women premenopausal by age for non-smokers who are not exposed passively to smoking (....); non-smokers who are exposed passively to smoking (— — —); and active smokers (—).

either effect is uncertain. The findings thus suggest that there is an effect from passive smoking but do not justify the conclusion that effects of active and passive exposure are equivalent. Further studies of larger populations are needed to confirm and further quantify these associations, consider the effects of additional potentially confounding variables (such as relative body weight) not studied here, and investigate possible transplacental effects.

We thank Dr Barbara S Hulka, department of epidemiology, University of North Carolina School of Public Health, for providing helpful advice at several stages of this study; Dr Jay H Lubin, environmental epidemiology branch, National Cancer Institute, for the computer program used for conditional logistic regression analysis; and Karen L Milne for helping in data management and analysis.

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(Accepted 7 July 1986)

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