the action of chlorpropamide with alcohol; alcohol with other sulphonylureas produces no such effects.

We have shown that CPAF is caused by opiate peptides such as enkephalin,² and we questioned whether these peptides also mediated the asthmatic reaction associated with CPAF. We found that asthma induced by chlorpropamide and alcohol was partially blocked in two patients by the specific opiate antagonist naloxone. One of these patients developed wheezing after an infusion of the enkephalin analogue DAMME. Thus asthma induced by chlorpropamide and alcohol is mediated by opiate peptides such as enkephalin.

Ethanol alone has not been reported to cause asthma. Some drinks containing ethanol induce wheezing in asthmatic patients, but this is caused by congeners since ethanol has no effect.³ The asthma induced by congeners is, however, similar to that induced by chlorpropamide and alcohol in several respects: there is a rapid fall in FEV₁ on challenge with the drink, which persists for about one hour; none of our patients described further wheezing up to 12 hours after challenge; and total IgE concentration and total eosinophil count did not change. Hence neither type of asthma is likely to be mediated by specific reaginic antibodies, though they may both be prevented by administering disodium cromoglycate.

CPAF, and by implication enkephalin, may act as a triggering factor in some asthmatic patients, though not every such patient who shows CPAF wheezes during the reaction. In a patient who showed CPAF (case 4) FEV₁ did not change after DAMME infusion or on challenge with chlorpropamide and alcohol. Several other non-immunological triggers cause asthma such as hyperventilation, cold air, exercise, emotional stress, and some chemical irritants, but the mechanism is uncertain. Some of these triggers may activate neural pathways, either by autonomic reflex or by stimulation of the central nervous system. Even allergen-induced asthma may be partially mediated by an autonomic reflex, since it is blocked in animals by vagotomy⁶ and atropine⁷ and in man by atropine.⁸ These observations have led to the suggestion that acute bronchoconstriction is largely caused by reflexes in lung receptors mediated by pulmonary afferent and bronchoconstrictor efferent pathways in the vagus nerve.

Many autonomic nerve fibres are neither cholinergic nor adrenergic but peptidergic. These fibres are rich in peptides

such as enkephalin that probably act as neurotransmitters.⁹ Asthma induced by chlorpropamide and alcohol might be mediated by a neurotransmitter effect of these peptides; alternatively such peptides might act locally as hormones—for example, carcinoid tumours produce similar peptides and can induce asthma and facial flushing.

We have described a new cause of asthma—that is, the interaction of chlorpropamide and alcohol. We believe that this asthma is mediated by peptides with opiate-like activity such as enkephalin. Although this type of asthma is rare, other factors causing release of enkephalins may have the same effect in patients susceptible to asthma.

We thank Dr B von Graffenried (Sandoz, Basle) for supplies of DAMME; Judith Pratt, Institute of Psychiatry, for assaying serotonin; and the chest unit technicians for their help. RDGL is supported by the Medical Research Council.

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References

- 1 Leslie RDG, Pyke DA. Chlorpropamide-alcohol flushing: a dominantly inherited trait associated with diabetes. *Br Med J* 1978;**2**:1519-21.
- 2 Leslie RDG, Pyke DA, Stubbs WA. Sensitivity to enkephalin as a cause of non-insulin dependent diabetes. *Lancet* 1979;**i**:341-3.
- 3 Stubbs WA, Delitala G, Jones A, *et al.* Hormonal and metabolic responses to an enkephalin analogue in normal man. *Lancet* 1978;**ii**:1225-7.
- 4 Yuwiler A, Plotkin S, Geller E, *et al.* Rapid accurate procedure for determination of serotonin in whole human blood. *Biochem Med* 1970;**3**:426-31.
- 5 Breslin ABX, Hendrick DJ, Pepys J. Effect of disodium cromoglycate on asthmatic reactions to alcoholic beverages. *Clin Allergy* 1973;**3**:71-82.
- 6 Gold WM, Kessler GF, Yu DYC. Role of vagus nerves in experimental asthma in allergic dogs. *J Appl Physiol* 1972;**33**:719-25.
- 7 Drazen JM, Austen KF. Pulmonary response to antigen infusion in the sensitized guinea pig: modification by atropine. *J Appl Physiol* 1975;**35**:916-9.
- 8 Yu DYC, Galant DS, Gold WM. Inhibition of antigen induced bronchoconstriction by atropine in asthmatic patients. *J Appl Physiol* 1972;**32**:823-8.
- 9 Guillemin R. Peptides in the brain: the new endocrinology of the neuron. *Science* 1978;**202**:390-402.

(Accepted 17 October 1979)

SHORT REPORTS

Follow-up study of rubella vaccination in general practice

An article¹ on the vaccination of rubella-susceptible women reported that out of 38 patients vaccinated only 25 appeared to have responded satisfactorily. As a result of this apparently low seroconversion rate further investigations were carried out. The feasibility of offering vaccination to rubella-susceptible women attending a contraceptive clinic has been stated.²

Method and results

Patients were asked by questionnaire about the brand of vaccine used, how long it had been in their possession, and whether kept in a refrigerator, handbag, or elsewhere. No difference in results was shown, but all had been supplied with Cendevax (Cendehill, Smith Kline & French). The 38 vaccinated patients had been bled to check the results of vaccination. All those with HAI titre of $\geq 1/80$ were considered to have an unsatisfactory response and those with some, but inadequate, immunity on first testing ($\leq 1/30$) that did not increase to $\geq 1/30$ after first vaccination were also considered unsatisfactory. Thirteen patients (19%) were considered to have an unsatisfactory response and it was decided to revaccinate them with RA27/3HT (a high-titre vaccine kindly made available to us by the Public Health Laboratory). The delay between the initial vaccination and revaccination of non-responders was between 30 and 42 weeks. A further sample of blood was therefore taken to check the initial findings and also

to see if the passage of time had raised the titre. Eight patients now had adequate titres—that is, ranging from 1/160 to 1/1280. Out of the five remaining patients, one still had no response but developed a titre of 1/320 after having RA27/3HT, and one had become pregnant and could not be revaccinated although her titre had risen only marginally from 1/20 to 1/40. All the remaining three had some immunity to start with, but inadequate by our advised criteria. Further time had made no difference to these and vaccinating with RA27/3HT only slightly raised the titres to 1/30, 1/40, and 1/80, respectively.

Comment

Thirty-eight patients with little or no immunity resulted in 13 inadequate responses to vaccination initially. Three of these were in patients with some antibodies, but at a low level, and their titres rose by very little after revaccination. Possibly this means that an antibody titre of 1/30 may in fact indicate adequate immunity against rubella as well as from the attenuated rubella in the vaccine. Of the other ten, only one definitely required vaccination. The response with the Cendehill strain is known to be slower than with RA 27/3 (Almevax B/W),³⁻⁵ so it should not be surprising that out of 13 original poor responders eight should subsequently have had adequate titres after more than six months. Possibly this indicates that the speedier response with Almevax might be more appropriate for general use.

Apparently very little benefit has been derived from checking immunity levels after vaccination. Only one patient out of 38 appears to have benefited. In terms of work load to the doctor, inconvenience

to the patient, expense incurred, and the possibility of repeated venepunctures having an adverse propaganda effect on the rubella immunisation programme it seems unjustified and unnecessary to extend the programme to include follow-up after vaccination. No harm seems to have been done to the potency of the vaccine by the patient keeping the ampoule in her handbag for many hours, but on the general principles of vaccine storage this should be discouraged. The time spent checking on patients has now eliminated the hitherto regular instances of worry for patients and doctors on alleged rubella contact in pregnancy.

I thank my secretary, Mrs Irene Williamson, for her help; my administrator, Mrs Janice Melling; and to Dr MacDonald and Dr Craske at the Public Health Laboratory, Withington, Manchester.

¹ Gringras M, Reisler R, Caisley J, Helliwell W, Bowker CH. Vaccination of rubella-susceptible women during oral contraceptive care in general practice. *Br Med J* 1977;2:245-6.

² Gringras M, Bowker C. Rubella susceptibility in women. *Br Med J* 1978;2:698.

³ Böttiger M, Heller L. Experiences from vaccination and revaccination of teenage girls with three different rubella vaccines. *J Biol Stand* 1976; 4:107-14.

⁴ Macdonald H, Tobin JO'H, Cradock-Watson JE, Lomax J. Antibody titres in women six to eight years after the administration of RA 27/3 and Cendehill rubella vaccines. *J Hyg* 1978;80:337-47.

⁵ Ingalls TH. Rubella vaccines and the immunity gap. *Lancet* 1979;1:831.

(Accepted 9 October 1979)

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Polycythaemia vera and central sleep apnoea

Secondary polycythaemia is a widely recognised complication of longstanding sleep apnoea.¹ It may be distinguished from polycythaemia vera by the absence of leucocytosis, thrombocytosis, and splenomegaly. In several cases sleep apnoea has occurred with neurological diseases and systemic illnesses known to have pathophysiological effects on central nervous system functioning.¹ While various neurological manifestations have been described in 56% to 78% of patients with polycythaemia vera, sleep apnoea has not been among them.² We recently studied a patient with polycythaemia vera and a subacute organic psychosis in whom central sleep apnoea responded to phlebotomy.

Case report

A 39-year-old man presented with a well-documented seven-year history of polycythaemia vera which had been confirmed by increased chromium-51 red blood cell volume, erythroid hyperplasia and absent iron stores in bone marrow, leucocytosis, raised leucocyte alkaline phosphatase activity, and normal arterial oxygen saturation. Initial clinical manifestations had been confined to malaise, headaches, phethora, and mild splenomegaly. During the last two years, however, he had had epistaxis, episodes of confusion on awakening, progressive difficulty in concentrating, and excessive daytime somnolence. During the month before admission to hospital his packed cell volume (PCV) had rapidly increased from 54% to 65%, accompanied by gross disorientation, memory loss, perseveration, and prominent delusions of guilt and annihilation. Bilateral papilloedema was present, although the remainder of the neurological examination was normal. Cerebrospinal fluid pressure was 280 mm H₂O. An exhaustive neurological and medical evaluation found no additional cause for these abnormalities, and waking respiratory function was normal. Polysomnography was performed both before phlebotomy and after reduction of his PCV to 48.8%. During this 10-day interval the confusional psychosis and papilloedema receded dramatically. Baseline studies had shown that frequent microarousals and decreased sleep efficiency were attributable to 52 episodes of central sleep apnoea, none of which occurred during rapid eye movement (REM) sleep. Apnoea occupied 14.1 minutes or 5% of total sleep time, with an average episode length of 16.3 seconds. Apnoea index (number of episodes per hour of sleep) was 8.9, compared with a published mean value for normal controls of 0.5.³ There was no evidence of an upper airway obstructive component to the sleep apnoea nor was it accompanied by cardiac arrhythmias. Follow-up sleep studies disclosed total disappearance of central sleep apnoea after phlebotomy. The patient has now remained free of neuropsychiatric symptoms and disordered sleep for one year with maintenance phlebotomy as his only treatment.

Comment

Although narcolepsy has been described in a few cases of primary polycythaemia,² we believe that this is the first reported case of central sleep apnoea complicating unequivocally diagnosed polycythaemia vera. Recognition of this potentially reversible cause of sleep apnoea is important, especially since it may be mistaken for the more commonly associated secondary polycythaemia. We further hypothesise that polycythaemia vera may lead to sleep apnoea through decreased cerebral blood flow to diencephalic respiratory centres. A similar mechanism has been proposed for other reversible neurological dysfunction described in this disorder.² Moreover, significant diminution of cerebral blood flow occurs even at PCV values often considered acceptable in the management of polycythaemia vera.⁴ The reason that apnoea never occurred during REM sleep may be that cerebral blood flow is increased during this stage of sleep.⁵

This work was supported in part by NIMH grants MH25642 and MH30915.

¹ Lugaresi E, Coccagna G, Mantovani M. *Hypersomnia with periodic apnoeas*. New York: Spectrum Publications, 1978.

² Silverstein A, Gilbert H, Wasserman LR. Neurologic complications of polycythemia. *Ann Intern Med* 1962;57:909-16.

³ Guilleminault C, Dement WC. *Sleep apnoea syndromes*. New York: AR Liss, 1978.

⁴ Thomas DJ, Du Boulay GH, Marshall J, et al. Cerebral blood-flow in polycythaemia. *Lancet* 1977;2:161-3.

⁵ Reivich M, Isaacs G, Evarts E, Kety S. The effect of slow wave sleep and rem sleep on regional cerebral blood flow in cats. *J Neurochem* 1968; 15:301-6.

(Accepted 10 October 1979)

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Massive arterial thrombosis and oral contraception

The relationship between oestrogen-containing contraceptives and venous thrombosis is well known. We report a case of widespread arterial thrombosis in a woman using a combined oral contraceptive pill.

Case report

A previously fit 33-year-old housewife was admitted to a local hospital after two grand mal fits. She smoked 40 cigarettes daily and had used oral contraception (Eugynon-30) for at least five years. Four days before admission she complained of headaches, upper abdominal pain, and vomiting. On examination she was drowsy, obese, had right hypochondrial tenderness, and a blood pressure of 220/140 mm Hg. Heart size and optic fundi were normal. Investigations: haemoglobin 14.7 g/dl, white blood count $24.3 \times 10^9/l$ ($24\,300/mm^3$), alanine aminotransferase 78 IU/l, lactate dehydrogenase 1319 IU/l, glucose 9.8 mmol/l (176 mg/100 ml), urea 3.0 mmol/l (18 mg/100 ml), amylase 60 IU/l. Radiographs of chest, skull, and abdomen were normal. Over the next few days her drowsiness cleared but a small right pupil, nystagmus, incoordination of right arm and leg, and impaired sensation over the left leg were noted. Tendon reflexes were absent in both legs. Cerebrospinal fluid and computed tomography of the head were normal. On day 3 the patient was anuric with absent femoral pulses. Blood pressure was now 140/90 and urea 19.5 mmol/l (117 mg/100 ml). On day 6 she was transferred to Withington Hospital in acute renal failure. Both legs were cold and pulseless. Bowel sounds were absent. Investigations: blood urea 40 mmol/l (240 mg/100 ml), creatinine 1.30 mmol/l (14.7 mg/100 ml), potassium 6.7 mmol(mEq)/l, haemoglobin 10.9 g/dl with fibrinogen degradation products of 19 mg/l (normal 6 mg/l), prothrombin time 15 s, thrombin-fibrinogen time 19 s, platelets $166 \times 10^9/l$ (166 000/ mm^3). Abdominal x-ray picture showed dilated loops of small bowel. Bilateral retrograde pyelograms were normal. A translumbar aortogram was unsuccessful, but an approach through the left axillary artery showed complete occlusion of the aorta to the level of T11. Mesenteric and renal arteries could not be filled. The electrocardiogram showed sinus rhythm with T-wave inversion in all chest leads. The patient remained anuric and died eight days after admission. Necropsy showed thrombus in the left ventricle with no evidence of myocardial infarction and healthy coronary arteries. The abdominal aorta was