

obstructed airways have an inappropriately low respiratory drive<sup>5</sup> and are susceptible to central nervous system depressants. Such patients may be identified by their arterial hypercapnia combined with the secondary effects of alveolar hypoventilation such as cor pulmonale, a raised plasma bicarbonate concentration, and polycythaemia. Morphine and barbiturates may have disastrous effects on ventilation in these patients<sup>6</sup> and even single doses of hypnotics such as nitrazepam, normally regarded as "safe," may cause profound respiratory depression.<sup>7</sup>

Ventilatory drive depends also on the hydrogen ion content of cerebrospinal fluid, and drugs that affect acid-base balance may therefore influence breathing. Thus the carbonic anhydrase inhibitors acetazolamide and dichlorphenamide produce an acidosis and may enhance respiratory drive.<sup>8</sup> By contrast, there is evidence that the benzothiadiazine and loop-type diuretics such as frusemide (which produce a hypokalaemic alkalosis) may reduce sensitivity to carbon dioxide.<sup>9</sup> This effect, however, is not universally accepted<sup>10</sup> and the theoretical disadvantages are balanced by the benefits that diuretics have on gas exchange when used in cor pulmonale and respiratory failure.<sup>11</sup>

Interestingly, sedatives are not always harmful either in patients with chronic airways obstruction. A recent study from Charing Cross Hospital records the effects of regular diazepam in four men who were severely disabled by breathlessness.<sup>12</sup> These "pink puffers" had disproportionate breathlessness, which is said to be a manifestation of their fight to maintain normocapnia.<sup>13</sup> Symptomatic relief in these patients (whose initial carbon dioxide tensions were normal) was not associated with a deterioration in their blood gases at rest. All four patients had previously been disabled by breathlessness and experienced "a striking reduction in dyspnoea and an improvement in effort tolerance." Clearly we need further studies on this type of patient; but we must not assume that diazepam would be safe for use in all pink puffers, particularly if their breathlessness appears to be appropriate to the degree of airways obstruction.

Whether beta-adrenoceptor antagonists affect respiratory drive is less clear. Mustchin and colleagues<sup>14</sup> have reported that propranolol reduces the ventilatory responses to carbon dioxide in normal people by almost a half, but subsequent studies<sup>15-18</sup> have produced conflicting results. Until these discrepancies have been resolved drugs like propranolol should be regarded as contraindicated in all patients with airways obstruction, irrespective of the reversibility of their effects by beta-adrenoceptor stimulants. Reassuringly, however, investigations on the effects of cardioselective beta-adrenoceptor antagonists such as atenolol and metoprolol have shown no effects on respiratory control.<sup>17,18</sup>

<sup>8</sup> Naimark A, Brodovsky DM, Cherniack RM. The effect of a new carbonic anhydrase inhibitor (dichlorphenamide) in respiratory insufficiency. *Am J Med* 1960;**28**:368-75.

<sup>9</sup> Iff HW, Flenley DC. The ventilatory response to CO<sub>2</sub> after administration of frusemide in normal man. *Clinical Science* 1972;**43**:47-54.

<sup>10</sup> Goldring RM, Cannon PJ, Heinemann HO, Fishman AP. Respiratory adjustment to chronic metabolic alkalosis in man. *J Clin Invest* 1968;**47**:188-202.

<sup>11</sup> Noble MIM, Trenchard D, Guz A. The value of diuretics in respiratory failure. *Lancet* 1966;ii:257-60.

<sup>12</sup> Mitchell-Heggs P, Murphy K, Minty K, et al. Diazepam in the treatment of dyspnoea in the 'pink puffer' syndrome. *Q J Med* 1980;**49**:9-20.

<sup>13</sup> Robin ED, O'Neill RP. The fighter versus the nonfighter. Control of ventilation in chronic obstructive pulmonary disease. *Arch Environ Health* 1963;**7**:125-9.

<sup>14</sup> Mustchin CP, Gribbin HR, Tattersfield AE, George CF. Reduced respiratory responses to carbon dioxide after propranolol: a central action? *Br Med J* 1976;iii:1229-31.

<sup>15</sup> Trembath PW, Taylor EA, Varley J, Turner P. Effect of propranolol on the ventilatory response to hypercapnia in man. *Clinical Science* 1979;**57**:465-8.

<sup>16</sup> Patrick JM, Tutty J, Pearson SB. Propranolol and the ventilatory response to hypoxia and hypercapnia in normal man. *Clinical Science and Molecular Medicine* 1978;**55**:491-7.

<sup>17</sup> Leitch AG, Hopkin JM, Ellis DA, Clarkson DMcG, Merchant S, McHardy GJR. Failure of propranolol and metoprolol to alter ventilatory responses to carbon dioxide and exercise. *Br J Clin Pharmacol* 1980;**9**:493-8.

<sup>18</sup> Folgering H, Braakhekke J. Ventilatory response to hypercapnia in normal subjects after propranolol, metoprolol and oxprenolol. *Respiration* 1980;**39**:139-43.

## Miraculous moles

Few outside a small circle of the cognoscenti in a highly specialised field took notice when three years ago Kajii and Ohama<sup>1</sup> reported a remarkable discovery that went far towards determining the cause of hydatidiform mole. They found that in molar pregnancies the chromosome complement, though apparently normal female (46,XX), consisted of two sets of paternally derived chromosomes without any maternal contribution. This male form of parthenogenesis (for so, in a chromosomal sense, it can be considered) is far more remarkable, not to say miraculous, than the development of a conceptus entirely from maternal sources.

The initial observations were based on banding studies on chromosomes of cultured and uncultured molar tissue and of the chromosomes of the mother and her partner. In seven cases in which the father's own two sets of chromosomes had different banding characteristics the banding patterns of the mole's sets were always identical with each other and with one of the paternal sets. This effectively ruled out dispermy (fertilisation by two sperms) as a mechanism and left two possibilities: fertilisation by a diploid (46 chromosome) sperm resulting from failure of cell division at second meiosis, or fertilisation by a haploid (23 chromosome) sperm which after meiosis duplicated its chromosomes without cell division. Confirmation of the initial observation came from other parts of the world, particularly the Pacific area, where the condition is so common.<sup>2-4</sup>

The usual chromosomal sex of complete hydatidiform moles is known to be XX; so the question that arose immediately was why the karyotype should be female if the chromosomes of these conceptuses were entirely derived from the father. The answer seems to be that diploid cells, unlike male haploid gametes, require the presence of at least one X chromosome in order to function; thus a cell deriving its 46 chromosomes from duplication of the 23 of a Y-bearing sperm would have the karyotype 46,YY and be non-viable.

Yamashita *et al*<sup>5</sup> reported on HLA types in 13 complete moles, and found both A and B types corresponding to those of

<sup>1</sup> Leitch AG, Clancy LJ, Costello JF, Flenley DC. Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. *Br Med J* 1976;ii:365-7.

<sup>2</sup> Lakshminarayan S, Sahn SA, Weil JV. Effect of aminophylline on ventilatory responses in normal man. *Am Rev Respir Dis* 1978;**117**:33-8.

<sup>3</sup> Sutton FD, Zwillich CW, Creagh CE, Pierson DJ, Weil JV. Progesterone for outpatient treatment of Pickwickian syndrome. *Ann Intern Med* 1975;**83**:476-9.

<sup>4</sup> Coppen AJ, Mezey AG. The influence of Sodium Amytal on the respiratory abnormalities of anxious psychiatric patients. *J Psychosom Res* 1960;**5**:52-5.

<sup>5</sup> Lourenço RV, Miranda JM. Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. *N Engl J Med* 1968;**279**:53-9.

<sup>6</sup> Wilson RH, Hoseth W, Dempsey ME. Respiratory acidosis. I. Effects of decreasing respiratory minute volume in patients with severe chronic pulmonary emphysema, with specific reference to oxygen, morphine and barbiturates. *Am J Med* 1954;**17**:464-70.

<sup>7</sup> Clark TJH, Collins JV, Tong D. Respiratory depression caused by nitrazepam in patients with respiratory failure. *Lancet* 1971;ii:737-8.

the father but not the mother; there was expression of only one pair of paternal A and B antigens, again pointing to likely origin from a single sperm. They suggested that hydatidiform moles resulted from "fertilisation" by a haploid sperm which subsequently duplicated its own chromosomes after meiosis; had a diploid sperm been produced at meiotic level HLA expression would probably have occurred for both paternal A and B antigen pairs in at least some cases.

Both polymorphic C-band features of chromosomes and HLA gene loci are, however, close to the centromere and therefore relatively inefficient markers for showing "cross-over." Lawler *et al*<sup>4</sup> reported further evidence supporting the haploid sperm origin using five enzyme markers in 11 complete moles. More recently Jacobs's group in Hawaii have reported studies<sup>6</sup> of phosphoglucomutase genotypes as well as chromosome banding in 20 moles and the parents concerned. Phosphoglucomutase is a better marker than HLA type since the gene responsible is probably more than five times further from the chromosome centromere than the HLA locus; again this study confirmed that in most cases the mole appears to arise from a haploid sperm.

Jacobs *et al*<sup>6</sup> found two "atypical" moles among the 24 they karyotyped. One was 46,XX but with evidence of normal maternal and paternal haploid contributions, while another was 46,XY, but its origin could not be determined. Apparently while most moles are male derived ("androgenetic") there are a few in which other explanations must be sought.

There is another part to the mystery: the loss of the maternal haploid contribution, and on this there are few clues. It is beyond biological credulity that no chromosomes are present at completion of the maturation of the ovum. They may either be lost before or at the time of "fertilisation" or be driven out by the double male sets before the first mitotic cell division. There is some evidence that mothers who have molar pregnancies have an increased incidence of reciprocal translocations,<sup>1</sup> and such structural abnormalities may possibly be responsible for the ovum nucleus failing to persist.

All these remarks apply to the common type of complete mole; but hydatidiform moles are now usually divided into two types<sup>7</sup>: in complete (or classical) moles the conceptus consists of hydropic, hyperplastic villous tissue but no fetus is present, the usual chromosome complement being 46,XX with two sets of identical paternal haplotypes; in partial moles there is focal trophoblastic hyperplasia and a range of dropsical villi, associated with the presence of a fetus. For some considerable time partial moles have been known to be associated with chromosome abnormalities—particularly the presence of an extra set of chromosomes—triploidy (69,XXX or XXY).

The source of the extra chromosome set in the triploid incomplete moles was found to be male in three out of three cases studied, but the paternal haploid sets were not identical. In two instances the evidence pointed to double fertilisation (dispermy), while the third could have been due to dispermy or failure of the first paternal meiotic division.<sup>4</sup> Both types of moles, therefore, seem often to have an extra set of paternal chromosomes—identical in the complete type and non-identical in the partial form. Not by any means all triploid conceptuses develop into partial moles—they often terminate as early spontaneous abortions<sup>4</sup>—while initial reports of dispermic conceptions concerned intersexual (46,XX/46,XY) chimeras.<sup>8</sup> While the complete moles have no mother in a chromosomal sense, the dispermic partial moles could possibly have two fathers, given maternal promiscuity.

These remarkable discoveries are important far beyond the field of reproductive biology. Trophoblastic neoplasia, of which

hydatidiform mole can be regarded as the simple but pre-malignant form, is still a major problem in many parts of the world despite advances in chemotherapy, and these new discoveries may prove important. The risk of a mole undergoing transformation to chorionic carcinoma<sup>9</sup> is greater in the complete than the partial variety, but there is not sufficient evidence at present to say malignancy may not develop with partial forms. The new knowledge is also likely to be relevant to the well-known propensity for pre-eclampsia to develop in association with hydatidiform mole, and it may provide important clues in the tantalisingly difficult task of elucidating the cause of pre-eclampsia. A theological student who turns his attention to this information must get ample food for thought, while a jurist specialising in parentage cases could find much material calculated to astonish the judges.

- <sup>1</sup> Kajii T, Ohama K. Androgenetic origin of hydatidiform mole. *Nature* 1977;268:633-4.
- <sup>2</sup> Jacobs PA, Hassold TJ, Matsuyama AM, Newlands IM. Chromosome constitution of gestational trophoblastic disease. *Lancet* 1978;ii:49.
- <sup>3</sup> Wake N, Takagi N, Sasaki M. Androgenesis as a cause of hydatidiform mole. *J Natl Cancer Inst* 1978;60:51-7.
- <sup>4</sup> Lawler SD, Pickthall VJ, Fisher RA, Povey S, Evans MW, Szulman AE. Genetic studies of complete and partial hydatidiform moles. *Lancet* 1979;ii:580.
- <sup>5</sup> Yamashita K, Wake N, Araki T, Ichinoe K, Makoto K. Human lymphocyte antigen expression in hydatidiform mole: androgenesis following fertilisation by a haploid sperm. *Am J Obstet Gynecol* 1979;135:597-600.
- <sup>6</sup> Jacobs PA, Wilson CM, Sprenkle JA, Rosenshein NB, Migeon BR. Mechanism of origin of complete hydatidiform moles. *Nature* 1980;286:714-6.
- <sup>7</sup> Szulman AE, Surti U. The syndromes of hydatidiform mole. II Morphologic evolution of the complete and partial mole. *Am J Obstet Gynecol* 1978;132:20-7.
- <sup>8</sup> Bain AD, Scott JS. Mixed gonadal dysgenesis with XX/XY mosaicism: the evidence for the occurrence of fertilisation by two spermatozoa in man. *Lancet* 1965;i:1035-9.
- <sup>9</sup> Vassilakos P, Riotton G, Kajii T. Hydatidiform mole: two entities. A morphologic and cytogenetic study with some clinical considerations. *Am J Obstet Gynecol* 1977;127:167-70.

## Assessment and management of adults with enuresis

Enuresis has been described as a normal reflex act of micturition that occurs during sleep.<sup>1</sup> As many as one in every 50 adults aged 16 have problems with bed wetting<sup>2</sup>; at that age women are affected as often as men, in contrast to the male preponderance during childhood.<sup>3</sup> The causes include both neurophysiological and behavioural factors.<sup>4</sup>

Three groups of patients may be identified. In the first, most adults give a history not only of lifelong enuresis but also of frequency of micturition with urgency and occasional urge incontinence by day. The terms enuretic syndrome<sup>5</sup> and diurnal/nocturnal enuretic<sup>6</sup> have been applied to these patients. Some will improve spontaneously up to the age of 30, but beyond that they tend to experience persistent diurnal symptoms and nocturia that wakens them. The second group of adults with primary enuresis have bed wetting alone and no diurnal symptoms. They usually have a good prognosis, as the condition normally resolves by the age of 25. The third group are the recurrent or secondary enuretics, who have relapsed after a period of being completely dry at night. In many such cases the problem seems to be a latent abnormality that may be exposed by excessive intake of fluid, such as beer drinking.<sup>3</sup>

The history and clinical examination usually differentiate