A Further Hazard of Intravenous Therapy?

Modern technology coupled with a little manual dexterity permits ready access to human blood vessels so that drugs and fluids can be administered and pressures recorded. While there is little doubt that these techniques have helped to reduce mortality in critically ill patients many types of iatrogenic disease have resulted: volume overload,[1] air embolism,[2] local damage to vessels with resulting thrombosis,[3] and sepsis[4] are well-recognized complications.

Traditionally, blood and other fluids for intravenous use have been administered from glass bottles, but they are difficult to store, they crack, and the rubber bungs may act as a nidus for infection.[5] When bungs and bottles are reused particles of rubber may become dislodged and form emboli. These difficulties—and the shortage of glass containers—have led to more widespread use of pliable storage bags made of polyvinylchloride (PVC) plasticized with esters of benzene dicarboxylic acid (phthalic acid). The most widely used plasticizer is di-2-ethylhexyl phthalate (DEHP), which may constitute up to 40% of the dry weight of vinyl plastics in current medical use.[6] Early laboratory studies indicated that DEHP had an extremely low toxicity,[7] but this conclusion was questioned when it was shown that plastics used in medical practice had a cardiodepressant effect.[8] Further doubts were cast on the safety of DEHP when it was shown to have accumulated in the tissues of two patients who had received blood transfusions during their terminal illness.[9] Later it was found that DEHP given intravenously accumulates in the lungs[6] and that urinary elimination is slow. In addition DEHP is partially metabolized to phthalic acid and an alcohol, 2-ethyl hexanol,[6 10] both of which are more toxic than the parent compound.

Though at first sight these findings are alarming, there are only a few clinical occasions in which quantities of DEHP of any practical importance could enter the systemic circulation. These include transfusion with blood which has been stored for 48 hours or longer,[11] extracorporeal circulation during cardiopulmonary bypass or haemodialysis,[12] and umbilical catheterization in neonates.[13] Recently Hillman and her colleagues have found DEHP in cardiac muscle and gut residues of infants dying of necrotizing enterocolitis—a condition which predominantly affects small, premature babies but may also occur in full-term infants after exchange transfusion. The latter association has led to suggestions[13] that DEHP might produce intravascular coagulation. Though this hypothesis is plausible it seems more likely that intravascular coagulation follows sepsis or excessive intravascular pressure during the exchange procedure. It is reassuring that recent studies[14] have failed to show that phthalates have any effect on platelet function; furthermore, the cardiodepressant effect of substances leached from older types of PVC tubing was probably related to the stabilizers rather than to DEHP.[15] Nonetheless, it is clear that further investigations of potential vascular toxic effects of DEHP and other plasticizers will be needed before they can be regarded as totally safe. Until such information is available the use of PVC containers and cannulae should be restricted to well-defined clinical indications.

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Early Thymectomy for Myasthenia Gravis

It has long been recognized in Britain that the earlier thymectomy was performed in myasthenia gravis the better the prognosis.[2] There was, however, for many years a natural reluctance to submit patients whose symptoms were readily controlled with anticholinesterase drugs to an operation which carried a definite mortality. More recently the risks of thymectomy have been dramatically reduced as a result of advances in the management of ventilatory failure with assisted respiration and the better recognition of myasthenic and cholinergic crises, and as the numbers of patients undergoing operation have increased its benefits have become more apparent. The incidence of remission increases with the number of years after thymectomy. Perlo *et al.*[2] in Boston and New York reported complete remission or substantial improvement in 84% of 45 women with severe myasthenia without a thymic tumour. Edward and Wilson[3] found improvement in 80%, and Papatestas and his colleagues[4] found that five years after thymectomy 90% of their patients were in remission or had shown considerable improvement.

The indications for thymectomy are, therefore, expanding to include milder cases and patients with earlier disease. In a recent review[5] of progress in myasthenia the indications for surgery at the various major centres concerned with the care of myasthenic patients was quoted. At the Mount Sinai Hospital, New York, with experience of 185 patients with myasthenia, the indications for surgery in patients without a tumour were an increasing need for anticholinesterase drugs or a poor response to medication.[4] The indications prompting thymectomy in Liverpool were severe weakness and incapacity despite anticholinesterase therapy, recurring respiratory infections leading to one or more incidents of myasthenic or cholinergic crises, and recently the operation has been advised for married women with hopes of having children.[3] At the New End Endocrine Clinic (now at the New Royal Free Hospital) over 260 patients with myasthenia gravis have been treated and thymectomy was offered to most of these, with the exception of patients with the purely ocular form of the disease.[5]

A new study from Mount Sinai Hospital[6] has emphasized the value of early surgery. Genkins *et al.* have experience of 353 patients who have undergone thymectomy, and their evidence shows that the duration of disease and the presence of germinal centres within the thymus gland influence the response to operation. The shortest interval between thym-

ectomy and complete remission occurred in patients with no germinal centres and a short history of disease. Indeed electromyographic studies showed immediate postoperative improvement in 60% of patients with no germinal centres and short duration of symptoms, whereas no immediate improvement was seen in patients with many germinal centres and a long history. They regard their findings as an indication for early thymectomy, while the disease is still in its mild stages. Since young patients have a higher incidence of germinal centres in the thymus thymectomy is particularly relevant to this age group—and as long ago as 1958 Simpson[7] stated that the best response to thymectomy was in young patients with a short history of disease. Furthermore thymectomy arrests the progress of the disease even when it fails to induce remission, so that early operation should reduce the number of patients developing the more severe forms of myasthenia. Similarly, in those patients with tumours of the thymus early operation is also indicated: the longer the duration of symptoms before surgery the greater the incidence of malignant change in the tumour.

Most of the conclusions reached by the Mount Sinai group will receive general acceptance, as they support what has been a clinical impression for some time. Similarly their recommendation that corticosteroids should follow and not precede thymectomy is sound advice. More controversial, however, is their claim that thymectomy via the transcervical approach should be regarded as the treatment of choice, owing to its low morbidity and negligible mortality. The low morbidity and mortality is surely due to the advances in anaesthesia and assisted respiration, which are now just as much features of the traditional approach through the sternum; and the traditional approach retains its advantage—the surgeon can actually see what he is doing.

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The Mite and Childhood Asthma: Myth or Menace?

Is the house-dust mite really a major allergen and responsible for symptoms in children with allergic asthma? Any such claims demand careful consideration as asthma is the commonest handicapping disease of childhood; the most recent British survey[1] showed that about 1 in 20 schoolchildren suffered from the disease. An allergic component can be shown in the vast majority of cases by positive reactions to simple skin tests with common known allergens. Frequencies of positive skin tests as high as 80% to house-dust and house-dust mite have been recorded in several surveys of asthmatic children.[2–4] But what further evidence is there to establish the mite as a major offending allergen, such as the evidence which already exists for grass pollen? Positive evidence should include opportunities for exposure, evidence of clinical sensitization, and the effectiveness of specific therapy.

The association of the mite *Dermatophagoides* spp. with human environs has now been established throughout the world.[5–7] The highest levels of infestation occur in the home, especially in the dust of beds and bedrooms;[8] lower levels have been found in institutions such as hospitals.[6] The particular distribution of the mite probably reflects its needs for human skin scales as a food source and its preference for warmth and humidity.[7] Fortunately it does not parasitize the human body.

Evidence that asthmatic children readily become sensitized to the house-dust mite has accumulated from studies using skin tests, nasal and bronchial provocation tests, and the detection of mite-specific IgE in sera.[2 4] It has also been shown that sensitization may occur as early as the second year of life,[2] probably as a result of the ample opportunities for early exposure to this ubiquitous allergen. The extrapolation of data obtained from these somewhat indirect methods to the incrimination of the mite as a major cause of allergic wheezing may, however, be questioned. Comparison with grass pollen hypersensitivity is again useful. Very small amounts of either allergen when inhaled can provoke symptoms in sensitive subjects; indeed McAllen *et al.*[9] estimated from quantitative bronchial challenge tests that allergenic material weighing less than one whole live mite could provoke an acute attack of asthma. Furthermore the measured serum levels of specific IgE provoked by these two allergens have been found to be roughly equivalent.[10] Mite allergy should, therefore, be considered as a factor in the causation of wheezing in childhood.

Therapy directed against any specific allergy must firstly aim at avoidance of the offending allergen. Complete eradication of the mite allergen is clearly impossible. A reduction in levels of mite infestation by the use of known chemical pesticides is already feasible, but the safety of these agents for asthmatic patients has yet to be established. A further problem is that the remains of dead mites and mite faeces and secretions retain their allergenicity. At present practical efforts at reducing inhalation of mite dust are limited to simple hygienic measures in the child s bedroom. These include regular vacuum cleaning, the use of synthetic bedding material, which should be washed frequently, and the enclosure of the mattress in an impervious cover. In a recently reported trial of the effectiveness of such avoidance measures Sarsfield and his colleagues[11] in Leeds showed that they can indeed greatly reduce the incidence of asthmatic attacks in mite-sensitive children. These cheap and harmless measures certainly warrant an initial trial in all asthmatic children with evidence of mite sensitivity.

A few trials of hyposensitization to the mite, using various dosage schedules and preparations, have so far been reported.[12–18] Their results indicate only limited success. The effectiveness of commercially available preparations has not yet been supported by clinical trials in mite-sensitive asthmatic children. Until these are reported, they cannot be recommended for routine therapy.

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