Discussion

The results clearly suggest that part of the poor correlation between F.E.V.$_1$ and $P\bar{v}CO_2$ may be explained by differences in personality between patients. Those who are highly extravert would appear to be more likely to have a lower $P\bar{v}CO_2$ at any F.E.V.$_1$ than patients who are more introvert. The relation between F.E.V.$_1$ and $P\bar{v}CO_2$ would appear to be independent of neuroticism, and this difference in results between E and N scores lends support to the validity of the inventory, which has suceeded in virtually abolishing any correlation between E and N scores.

Eysenck (1960) postulated that the N score is closely related to an inherited degree of lability of the autonomic nervous system, while the E score is related to the degree of excitation prevalent in the central nervous system. The correlation between $P\bar{v}CO_2$ and E score may therefore reflect changes in the excitability of the respiratory motor neurones, so that the motor output in patients with a high E score is greater for any input than those with lower E scores. Thus the differences in E score may explain the change in central sensitivity that has been postulated.

There are a number of unresolved problems. Is the correlation between E score and $P\bar{v}CO_2$ a secondary or primary phenomenon? If a secondary phenomenon, what is the mechanism for the change in excitability of respiratory motor neurones? Both these problems require examination, but at this stage it is possible to reconcile the dilemma about the correlation being a primary or secondary effect. Such a reconciliation is based on the proposal that there is an inverse relation between E score and the ability to be conditioned. From such a consideration it may be postulated that healthy individuals with a low E score are more readily conditioned and thus, in face of the stress of hindered breathing, are more likely to develop a tolerance to raised $P\bar{v}CO_2$ caused by difficulty in CO_2 elimination. This tolerance is mediated by a reduction in the excitability of respiratory motor neurones which is manifest by a fall in ventilatory response to CO_2.

The correlation between E score and $P\bar{v}CO_2$ may also reflect the correlation between E score and other factors that may be important. For example, smoking is thought to be related to personality traits, and smoking habits may introduce bias if smoking, personality, and emphysema, for example, were intercorrelated. Our study was not designed to examine this problem, and the sample size was too small to show significant differences in smoking habit to allow further analysis. It is also possible that the E score might be related to clinical subgroups—for example emphysema. Any such correlation, however, must take cognizance of the fact that clinical correlations are weak and that we used the actual—predicted $P\bar{v}CO_2$ to help decide whether patients had emphysema. Any correlation between emphysema and E score might therefore be caused by their common correlation with actual—predicted $P\bar{v}CO_2$. These discussions can make more sense if the causation of CO_2 retention is postulated as being multifactorial. Thus the mechanical abnormality of airways obstruction, the central sensivity to input stimuli, the nature of the pathological abnormality, the environment, and the personality may all play a part in the genesis of CO_2 retention. We have confined our attention so far as was possible to the personality, but fully acknowledge that this is only one of a number of factors that may be important.

It is now necessary to find ways of studying the relation between personality and airways obstruction in the healthy subject. Whether or not the correlation between E score and $P\bar{v}CO_2$ is primary or secondary, it would be appropriate to refer to "pink puffers" as "pugnacious pink puffers" if such an appellation is found to be useful.

We wish to thank Dr. G. W. Scott for allowing us to study patients attending the chest clinic. We owe special thanks to Miss Margaret Gray, who provided invaluable technical assistance.

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Preliminary Communications

Malignant Hyperpyrexia during Anaesthesia: Possible Association with Subclinical Myopathy

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Summary: The members of a family in whom three malignant hyperpyrexial deaths occurred during anaesthesia were studied by means of serum creatine phosphokinase estimations. Abnormally high levels were found in many asymptomatic relatives. It is suggested that the abnormal levels reflect a subclinical myopathy of autosomal dominant inheritance which possesses a potentially lethal propensity resulting in a malignant hyperpyrexia when challenged with various anaesthetic agents. Possibly sudden unexplained deaths under varying circumstances are a further expression of this underlying abnormality.

A possible clue to the anticipation of future cases of malignant hyperpyrexia has been found, and it is suggested that relatives of previous cases be investigated.

Introduction

Over the past decade the syndrome of malignant hyperpyrexia (Denborough and Lovell, 1960) during anaesthesia has been well documented, so that Wilson *et al.* (1967) were able to quote 28 cases from the literature and add a further 12 unrecorded cases which they had collected from various hospitals. Malignant hyperpyrexia was the subject of a leading article in the *British Medical Journal* (1968). To date over 120 cases have been documented or quoted (Britt and Gordon, 1969). The hyperpyrexial reaction occurs during anaesthesia which in many instances has been given for a minor surgical procedure in an otherwise healthy individual. With few exceptions, over the past 10 years the anaesthetic used has consisted of halothane, nitrous oxide, and oxygen, induction being by either sodium thiopentone or nitrous oxide and halothane. All of the halogenated hydrocarbon inhalants, however, have been incriminated. Suxamethonium, again with few exceptions, was the relaxant used to facilitate intubation.

The first indication of an untoward reaction is often tightness of the jaw muscles. This is an important sign which must not be overlooked, as further suxamethonium administration accelerates the muscle damage. Later, during the anaesthesia, the patient becomes cyanosed, and this is associated with a

progressive hyperpyrexia, levels of up to 112°F. (44·4°C.) having been recorded. In addition there is pronounced tachycardia, mottling of the skin, and, with very few exceptions, severe generalized muscle spasm. The overall mortality rate has exceeded 70%. There have been a few survivors, presumably when the reaction has not been as fulminating or when the condition has been detected at an early stage and treated by immediate cooling, hyperventilation with 100% oxygen, and correction of the acidosis and hypovolaemia with intravenous sodium bicarbonate (Denborough and Lovell, 1960; Wilson *et al.*, 1967; Britt and Gordon, 1969) and fluid replacement. Further investigations carried out in some cases have shown severe hyperkalaemia and myoglobinuria, as was found in the third case recorded below, where, in addition, the serum aldolase level was raised to 1,200 units (normal 0-40 i.u.).

The cause of the hyperpyrexia is unknown. Wilson *et al.* (1966) postulated a disturbance of oxidative phosphorylation, but this is not acceptable as at least 75% of the heat produced comes from anaerobic sources (Berman *et al.*, 1969). Mitochondrial degeneration has been noted (Britt *et al.*, 1969), but this is probably a secondary phenomenon. The primary abnormality, however, is thought to be muscular.

Present Study

In 1962 a case of malignant hyperpyrexia during anaesthesia with fatal outcome occurred at Coronation Hospital, Johannesburg. A second case occurred the following year. The kinship of these two patients was noted, and one of us (M.B.B.) warned other members of the specific risk of general anaesthesia to their family (Barlow and Isaacs, 1970). Despite these warnings a third member suffered a similar death a year later. At this time several members of the family were studied clinically and electromyographically with negative results. There was no evidence of myotonia.

It was decided to reinvestigate the family by means of serum enzyme studies. The family is of mixed Caucasian and African extraction. Since a good correlation exists between serum creatine phosphokinase and aldolase at both high and low levels, aldolase determinations were considered unnecessary and were dropped in favour of the more sensitive serum creatine phosphokinase.

A surprising number of abnormally high levels of serum creatine phosphokinase were recorded in the resting state. In some cases the levels were as high as 800 units (normal values 0-50 for males and 0-30 for females). To date more than 100 members extending over three generations have been studied. The serum creatine phosphokinase estimations have shown a subclinical abnormality which is inherited as a Mendelian dominant trait with variable penetrance.

A further point of interest is that a number of sudden and unexplained deaths have occurred in this family. Though the high enzyme cases so far have not been associated with any obvious muscle weakness or other clinical abnormality, comprehensive studies are being carried out and will be reported later.

Discussion

The familial occurrence of malignant hyperpyrexia during anaesthesia is of particular importance as it implies an inherited defect which predisposes susceptible individuals to this type of reaction when challenged with chemicals commonly used in anaesthetics. Denborough *et al.* (1962) reported 10 deaths as a result of general anaesthesia occurring out of a total of 24 anaesthetics given to members of a particular family. The anaesthetic agents used were suxamethonium/nitrous-oxide/halothane in one case and ether and ethyl chloride in the remainder. In this latter group retrospective information was limited, but anoxia and hyperpyrexial deaths were established in two, while the patient receiving suxamethonium/nitrous-oxide/halothane survived an anticipated hyperpyrexial reaction. They suggested that the abnormality was transmitted as an autosomal dominant. Stephen (1967) reported an additional case and commented that "an as yet undetected constitutional or genetic abnormality may be responsible for the syndrome." Several other familial examples have been published. The most important is that of Britt *et al.* (1969), who demonstrated the trait for malignant hyperthermia in three successive generations and described the pattern of inheritance as autosomal dominance with a reduced penetrance and variable expressivity.

The presence of a genetically determined propensity to develop malignant hyperpyrexia was strengthened by the finding of susceptible laboratory animals. Malignant hyperpyrexia was reported in pig litter-mates after halothane/oxygen induction and suxamethonium administration (Hall *et al.*, 1966). A similar response was found in a strain of Landrace pigs (Harrison *et al.*, 1968).

The literature on suxamethonium-induced myoglobinuria (Bennike and Jarnum, 1964), together with our own experience in this problem, has shown that suxamethonium and/or halothane cause muscle damage as reflected by the rise in serum creatine phosphokinase (Tammisto and Airaksinen, 1966). Repeated administrations of suxamethonium in the same anaesthetic seem to have a potentiating effect and myoglobinuria occurs in the more severely affected cases. As both halothane and suxamethonium have been shown to affect the muscle or, perhaps, the muscle cell membrane adversely, we thought that malignant hyperpyrexia might occur in response to challenging an already abnormal muscle membrane with these anaesthetic agents. The serum creatine phosphokinase results have confirmed the presence of a widespread subclinical abnormality in the family at risk.

These findings raise several important issues. The occurrence of malignant hyperpyrexia and high serum creatine phosphokinase levels in one family is unlikely to be coincidental. This occurrence is placed beyond the realms of coincidence by the fact that one of us (H.I.) recently examined a further patient from another family who survived a malignant hyperpyrexial reaction and observed a serum creatine phosphokinase level of 400 units in an asymptomatic sister. The families are unrelated so far as we know.

If one accepts the occurrence of malignant hyperpyrexia and abnormal serum creatine phosphokinase levels as manifestations of a muscle abnormality, then it is possible that those asymptomatic patients with the highest levels of serum creatine phosphokinase are the greatest anaesthetic risks. If this hypothesis is acceptable it becomes an urgent matter that all close relatives of known cases of malignant hyperpyrexia be investigated for serum creatine phosphokinase abnormality. Furthermore, the high incidence of unexplained sudden deaths must also be considered in this light, as it may be that malignant hyperpyrexia is only one way that this potentially lethal trait finds expression. The fact that malignant hyperpyrexia has been recorded only in young people, the oldest aged 47 years, supports this view.

Finally, it should be appreciated that high levels of serum creatine phosphokinase may be found in a condition other than muscle dystrophy, polymyositis, muscle damage, etc., and, since they may occur in asymptomatic carriers of the malignant hyperpyrexial reaction, this could lead to difficulties with genetic counselling in some instances.

The serum creatine phosphokinase estimations were done by Dr. I. Bersohn of the South African Institute for Medical Research. We are indebted to the Institute and to Dr. Bersohn in particular.

H. ISAACS, M.D., DIP.MED., M.R.C.P.ED.
Physician Department of Physiology, Witwatersrand University Medical School, Johannesburg.

M. B. BARLOW, F.F.A. R.C.S.I.
Associate Professor, Department of Anaesthetics, Coronation Hospital, Johannesburg.

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Medical Memoranda

Polyarteritis Presenting with Leg Pains

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Polyarteritis (polyarteritis nodosa) is a multi-system connective-tissue disorder involving small and medium-sized arteries throughout the body. Occasionally, however, the condition is clinically localized to a few systems, such as skin and muscle, and it appears that in these circumstances the disease often follows a relatively benign course (Rose, 1957; Rötstein and Good, 1958).

In this paper three cases of polyarteritis are presented in which the initial and predominant symptoms were pains in the legs. In two patients the lesions were confined to the skin and muscles of the lower limbs, and in the third the arteritis appeared to be localized entirely to the leg muscles, a finding not previously described in the literature.

CASE 1

For several years a 47-year-old Italian man had been subject to attacks of pain in alternate legs lasting for two to three days and usually associated with the appearance of a rash. When seen during the course of a typical attack he had a mild pyrexia (99-100°F.; 37·2-37·8° C.), tenderness on palpation of the calf muscles, and an erythematous rash on the legs. The E.S.R. was 54 mm./hour (Westergren), and electrophoresis of serum proteins showed raised alpha-2 globulin. Laboratory investigations: urine and blood urea normal; haemoglobin 85%; W.B.C. 13,800/cu. mm., 79% polymorphs; and rheumatoid factor, antinuclear factor, and L.E. cells negative. Chest radiographs, intravenous pyelogram, and electrocardiogram showed nothing abnormal.

Biopsy of a skin lesion showed a subacute perivascular reaction in the dermis associated with some oedema. Polymorphs were frequent among the cells, and the appearance suggested polyarteritis. Biopsy of a calf muscle was normal, as were the muscle serum enzymes, but electromyography showed changes consistent with a muscle fibre lesion.

The symptoms were completely suppressed by prednisolone 22·5 mg. daily. When he attempted to reduce the steroid dose the pain recurred, but after some months it was possible to reduce to prednisolone 10 mg. and later 5 mg. daily without recurrence of pain. On this dosage he has been well to the date of follow-up, 18 months from the onset of symptoms.

CASE 2

A 30-year-old male charge nurse had been affected by mild generalized "rheumatism" for some years. For the previous three months he had complained of gradually increasing pains in the legs which were aggravated by standing and walking, and had noticed red tender lumps on the legs. On examination there was pronounced tenderness of the calf muscles, but no other abnormalities. Investigations showed: urine and blood urea normal; haemoglobin 88%; E.S.R. 5 mm./hour; W.B.C. 8,200/cu. mm., normal differential. Electrophoresis of serum proteins showed raised alpha-2 globulin; serum muscle enzymes showed raised lactic dehydrogenase; and rheumatoid factor, antinuclear factor, and L.E. cells were negative.

Biopsy of a skin lesion showed normal epidermis and perivascular infiltration with round cells in the dermis, some vessels showing panarteritis and areas of necrosis. Muscle biopsy was not carried out on this patient and electromyography on the calf muscles showed mild patchy myopathic changes.

Soon afterwards his symptoms settled without any specific treatment. During subsequent years, however, he was troubled at times with calf pains, which were sometimes accompanied by a rash on the legs. The pains were always effectively relieved by large doses of aspirin (up to 18 tablets daily). Three years later he was given prednisolone 5 mg. daily in an effort to reduce the frequency and severity of the attacks of leg pain, but this did not appear to modify the symptoms. To date he has remained well in himself and has developed no other manifestations of generalized connective-tissue disease.

CASE 3

In 1961 a 40-year-old decorator had for six months noticed stiffness and later pain in the calves, first on one side and then on both, not accompanied by a skin eruption. The pain became progressively more severe and eventually he had to walk on tip-toe as he was unable to put his heels to the ground while keeping his knees straight. Examination showed brisk knee-jerks and ankle-jerks, flexor plantar responses, normal sensation, and pronounced calf tenderness. Electromyography at this stage and on several later occasions showed no abnormality. The blood count, E.S.R., and electrophoresis were also normal, and a biopsy specimen of a calf muscle was reported as showing "subacute focal myositis." Though it was not possible at this time to make a certain diagnosis, he was given dexamethasone 1·5 mg. daily, as it was thought that he had a form of systemic connective-tissue disorder; his symptoms improved within a week. Five months later he stopped the drug of his own accord, and as he remained symptom-free this was not restarted.

He was then lost to follow-up, but returned two years later with recurrence of leg pains; he also had pain and tenderness in the thigh muscles. Investigations showed: urine and blood urea normal; haemoglobin 84%; W.B.C. 5,000/cu. mm., normal differential; E.S.R. 24 mm./hour; electrophoresis of serum proteins normal; rheumatoid factor, antinuclear factor, and L.E. cells negative; serum muscle enzymes normal; and skin biopsy normal. A calf muscle biopsy was again carried out: it showed panarteritis of medium-sized arteries, with disruption and atrophy of adjacent muscle fibres (see Fig. 1). Betamethasone 1·5 mg. daily was given, again with symptomatic relief, and he had to maintain this dose in order to remain symptom-free. He remained well until 1965 when he again defaulted, and has not been seen since.

DISCUSSION

These cases of polyarteritis illustrate that the disease may be confined to muscle and skin and that it may present with pain