local barrier to the diffusion of the tumour. As we have shown, however, the presence of metastases in regional nodes is not incompatible with a D+ or D++ score and long-term survival. Our results confirm those of other series on all histological types of breast cancer, particularly medullary carcinoma (Hamlin, 1968; Bloom *et al.*, 1970; Wernicke, 1972). Other workers have found no correlation between survival and sinus histiocytosis (Berg, 1956; Moore *et al.*, 1960; Kister *et al.*, 1969), follicular hyperplasia (Moore *et al.*, 1960), and lymphocytic infiltration (Morrison *et al.*, 1973) but we believe that the histology of both tumour and lymph nodes must be studied to obtain an accurate picture of host resistance. There is undoubtedly a close relationship between host immunological response and prognosis in the breast cancer. That this response is cell mediated was confirmed by Fisher *et al.* (1973), who showed that lymphocytes from lymph nodes draining a breast cancer were stimulated *in vitro* by phytohaemagglutinin. This transformation was associated with follicular hyperplasia and lymphocytic infiltration, whereas no clear-cut correlation could be shown with the presence or absence of sinus histiocytosis.

We believe that further studies of the immunological response of lymph nodes draining a tumour removed at operation would provide more information about prognosis (*Lancet*, 1973). At present we are correlating tumour lymphocytic infiltration and follicular hyperplasia and sinus histiocytosis in

regional lymph nodes with preoperative and postoperative lymphocytic responses to phytohaemagglutinin, aspecific and specific delayed cutaneous hypersensitivity reactions, and distribution patterns of T and B cells at tumour and lymph node levels.

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MEDICAL MEMORANDA

Malignant Hyperpyrexia Induced by Nitrous Oxide and Treated with Dexamethasone

F. RICHARD ELLIS, I. M. C. CLARKE,
T. N. APPLEYARD, R. C. W. DINSDALE

British Medical Journal, 1974, 4, 270-271

Though fever has been recognized as a complication of anaesthesia for over 80 years the specific condition of malignant hyperpyrexia has only comparatively recently been described. It is known that susceptible patients, who have been found to have a subclinical myopathy (Harriman *et al.*, 1973), develop a fulminating and often fatal hyperpyrexia when given certain anaesthetic drugs or depolarizing muscle relaxants (Britt and Kalow, 1970). A working definition of malignant hyperpyrexia is an unexplained fever during anaesthesia in which the body temperature rises at a rate of at least 2°C an hour (Keaney and Ellis, 1971). Most patients develop muscle contracture, acidosis, and hyperkalaemia. The condition is inherited as a Mendelian autosomal dominant.

Malignant Hyperpyrexia Investigation Unit, Department of Anaesthesia University of Leeds, Leeds LS2 9NL

F. RICHARD ELLIS, M.B., F.F.A. R.C.S., Senior Lecturer in Anaesthesia
I. M. C. CLARKE, M.B., F.F.A. R.C.S., Research Fellow

Department of Anaesthesia, University of Sheffield, Sheffield
T. N. APPLEYARD, M.B., F.F.A. R.C.S., Lecturer

Department of Dental Surgery, School of Clinical Dentistry, University of Sheffield, Sheffield

R. C. W. DINSDALE, B.CH.D., F.D.S. R.C.S., Consultant Dental Surgeon and Honorary Clinical Lecturer

The screening test for susceptibility to malignant hyperpyrexia (Ellis *et al.*, 1972) requires muscle tissue obtained by motor point muscle biopsy. The biopsy is performed under general anaesthesia for three reasons. Firstly, the procedure takes about 90 minutes, which is too long for conscious patients, especially children, to lie quietly. Secondly, if the local anaesthetic reaches the muscle tissue the identification of the motor point is impossible owing to the blockade of the motor nerve terminal, and, thirdly, the muscle test on living muscle *in vitro* is much less sensitive.

The general anaesthetic technique used involves intermittent thiopentone and nitrous oxide via a mask after diazepam premedication; recently fentanyl has been included. This regimen, which has proved satisfactory and uneventful in over 50 such patients, was felt to be safe because none of the drugs have ever been implicated in the induction of malignant hyperpyrexia. Intensive body temperature monitoring is mandatory.

We report here, however, a patient in whom nitrous oxide was shown conclusively to be responsible for the malignant hyperpyrexia episode under anaesthesia. The malignant hyperpyrexia was dramatically and successfully treated with dexamethasone.

Case Report

An 11-year-old apparently healthy girl required dental extractions. As her father had died of hyperpyrexia under anaesthesia for tendon suture during which he received thiopentone, suxamethonium, nitrous oxide, and halothane it was decided to investigate the patient for malignant hyperpyrexia susceptibility by muscle biopsy at the same time as the dental treatment. The patient was premedicated with diazepam, and anaesthesia was induced with thiopentone and maintained with 70% nitrous oxide and 30% oxygen via a mask. Body core temperature, measured with a rectal thermocouple probe, began to rise and after 12 minutes anaesthesia was abandoned as the rectal temperature had risen 1.2°C—that is, at a rate of 6°C per hour. An attempt to cool the patient with ice in the axillae, groins, and over the precordium and with cold water blankets failed. She was given

45 mg dexamethasone with dramatic results; the body temperature fell at a similar rate to the previous rise.

Dental extractions were not performed and her postanaesthetic course was uneventful apart from some body temperature instability for the first hour.

A few weeks later anaesthesia was induced, without premedication, with nitrous oxide and oxygen via a mask as it was thought that thiopentone might have been responsible for the hyperpyrexia on the previous occasion. Immediately her body temperature began to rise and anaesthesia was abandoned. The exposure to nitrous oxide on this occasion was very brief and the body temperature stabilized without active treatment.

One hour later anaesthesia was induced and maintained with thiopentone while the patient breathed oxygen only, and the dental extractions were performed uneventfully with a stable body temperature. The postoperative course was normal.

The patient's homozygous twin was given an uneventful thiopentone anaesthetic after diazepam premedication for dental extractions one month later.

Barlow and Isaacs (1970) have stated that patients susceptible to malignant hyperpyrexia have raised serum creatine phosphokinase levels, yet both this patient and her twin sister had serum creatine phosphokinase levels well within the normal range—46 IU/l. and 39 IU/l. respectively, and we have often found this (Ellis *et al.*, 1974).

Comment

The importance of these observations lies, firstly, in the direct implication of nitrous oxide in the production of malignant hyperpyrexia, and, secondly, in the effectiveness of dexamethasone in the treatment of the established condition.

Malignant hyperpyrexia has been reported with all volatile inhalational anaesthetic drugs which are usually administered with nitrous oxide as a carrier gas. Though nitrous oxide as an anaesthetic is of low potency it is rarely used on its own with spontaneous ventilation. Many patients who develop malignant hyperpyrexia receive anaesthesia for comparatively minor surgery, during which spontaneous ventilation with nitrous oxide and halothane is the rule. Therefore, it is often impossible to differentiate between the hyperpyrexia-inducing property of a volatile anaesthetic and of the nitrous oxide given concomitantly. To our knowledge there is no other report of malignant hyperpyrexia after nitrous oxide alone. Britt *et al.* (1974) report two patients who developed malignant hyperpyrexia with nitrous oxide and non-depolarizing relaxant anaesthetics and they believe that the relaxant was responsible for the hyperpyrexial reaction; our experience suggests that their interpretation may be incorrect.

Intravenous hydrocortisone 1-2 g has been used in several successful treatment regimens, but we are unaware of any successful management of malignant hyperpyrexia with dexamethasone (which is more convenient than hydrocortisone as it is already in solution and thus can be given without delay). The rapidity of the fall of temperature in our patient suggests that dexamethasone has a more specific effect than just producing peripheral vasodilatation and positive inotropism, which at best would only help heat loss. Further work on the possibly specific action of dexamethasone is in progress, but in a preliminary study of the effects of steroids on muscle taken from a patient

susceptible to malignant hyperpyrexia hydrocortisone in a clinically acceptable concentration (0.029 mmol/l.) abolished the halothane-induced contracture (fig. 1). Pretreatment of the muscle with hydrocortisone almost completely prevented the abnormal halothane-induced contracture (fig. 2). These findings further support the use of steroid therapy in the acute phase of malignant hyperpyrexia. Steroids of the dexamethasone and hydrocortisone type must, presumably, have a direct effect in controlling the abnormal muscle metabolism.

FIG. 1—Effect of hydrocortisone on halothane-induced contracture. H = Halothane 1% introduced into tissue bath. hc = Hydrocortisone 0.029 mmol/l. added to tissue bath.

FIG. 2—Effect of pretreatment with hydrocortisone on halothane-induced contracture. H-on = Halothane 1% introduced into tissue bath. H-off = Halothane washed out of tissue bath. a = Control. b = Specimen pretreated with hydrocortisone 0.029 mmol/l. c = Specimen pretreated with hydrocortisone 0.29 mmol/l.

In conclusion, we question the use of nitrous oxide in patients with a high probability of malignant hyperpyrexia under anaesthesia, especially if intensive temperature monitoring is not used, and we suggest that the first phase of treatment should include high doses of a steroid, such as dexamethasone 1-2 mg/kg, rather than procaine.

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