Other Fetal Damage

The possibility that oral anticoagulants produce fetal morbidity and mortality by means other than depression of vitamin-K-dependent clotting-factors requires serious consideration. It is possible that the 12 non-haemorrhagic fetal deaths reviewed by Villasanta (1965b) and mentioned above were due to vitamin-K antagonists. Some of the patients, however, had severe pulmonary embolism, and fetal death has also been reported in association with untreated pulmonary embolism (Blum and Barre, 1957). In addition, Runge and Hartert (1954) and Mertz and Breitner (1956) found no evidence of fetal damage in 12 women given coumarins between the second and fifth months of pregnancy before legal abortion. More recently nasal bone malformations have been reported in two cases where the mother was given warfarin in the first two months of pregnancy (Kerber *et al.*, 1968).

Four cases in our series (Nos. 1, 2, 11, and 14) were treated with anticoagulants during the first trimester, three with oral agents and one with heparin, with no evidence of fetal damage. These numbers, however, are small and certainly do not exclude the possibility that oral anticoagulants can produce effects on the fetus other than depression of coagulation factors. Hence these drugs, and indeed any drugs that cross the placenta, should be given in pregnancy only when there are firm indications. This is particularly so in the first trimester, when the risk of teratogenetic effects is at its greatest. Because of this, our present policy is to instruct women on oral anticoagulant therapy to report at the first possibility of pregnancy. If this is confirmed, treatment with warfarin is stopped and heparin is used until about 13 weeks' gestation.

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Effect of Personality on Alveolar Ventilation in Patients with Chronic Airways Obstruction

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Summary: A study has been made of the personality of 44 patients with chronic airways obstruction (using the Eysenck Personality Inventory), this being related to the difference between their observed $P\bar{v}CO_2$ and that predicted from their F.E.V.$_1$. This was designed to test the hypothesis that those patients with a lower $P\bar{v}CO_2$ than predicted were the more extravert.

The results showed a significant correlation between extraversion and the departure of $P\bar{v}CO_2$ from predicted Those patients having a lower $P\bar{v}CO_2$ than predicted were more extravert than those with a $P\bar{v}CO_2$ higher than predicted. There was no correlation between neuroticism and the $P\bar{v}CO_2$.

These results support the hypothesis that the personality of a patient may play an important part in determining the alveolar ventilation found in patients with chronic airways obstruction. Patients known as "pink puffers" could more appropriately be named "pugnacious pink puffers."

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Introduction

Patients with chronic airways obstruction are known to be liable to develop respiratory failure with CO_2 retention, but the factors responsible for CO_2 retention are not clear. The mechanical abnormalities associated with airways obstruction play an important part, but there is good evidence that they are not solely responsible for the appearance of CO_2 retention. This is witnessed by the poor correlation obtained between the forced expired volume in one second (F.E.V.$_1$) and the CO_2 tension (P_{CO_2}). Burrows *et al.* (1965) examined this correlation and obtained a regression equation that allows the P_{CO_2} to be predicted from the F.E.V.$_1$—namely,

$$\text{Mixed venous } P_{CO_2} = \frac{11{\cdot}5}{\text{F.E.V.}_1} + 36{\cdot}7$$

The most striking feature of the correlation is, however, its weakness, and many patients have a $P\bar{v}CO_2$ much lower or higher than the mean value predicted by the regression equation. The present paper is concerned with the reasons for this scatter.

Previous work has suggested that, in addition to the mechanical hindrance to breathing, changes in central responsiveness to CO_2 are associated with the presence of CO_2 retention (Clark, 1968). The reasons for this change in responsiveness are not clear, but attention has been drawn to the fact that those patients with a lower $P\bar{v}CO_2$ than predicted were more distressed and appeared to be "fighting" their disability (Robin and O'Neill, 1963) in contrast to the passive acquiescence displayed by many patients with apparently less airways obstruction and a higher CO_2 retention than predicted. We have examined the implications of this observation by postulating that the personality of an individual who develops airways obstruction in part determines the alveolar ventilation developed in face of the airways obstruction.

Methods and Material

Patients.—Forty-four patients with chronic airways obstruction were studied. All had an $F.E.V._1$ of less than 1·5 litres (mean=0·86 litre) and a ratio of $F.E.V._1$ to vital capacity less than 0·6 (mean=0·47). This sample of patients included those with asthma (7), chronic bronchitis (21), and those thought to have emphysema (16).

$F.E.V._1$ and Vital Capacity.—These measurements of ventilatory capacity were obtained with a dry bellows spirometer (Vitalograph). The mean of three attempts was taken and the vital capacity was recorded at the end of a forced expiration.

$P\bar{v}CO_2$.—The mixed venous P_{CO_2} was measured with a two-stage rebreathing procedure (Campbell and Howell, 1960).

Personality.—The personality was measured with the Eysenck Personality Inventory, which is a development of the Maudsley Personality Inventory (Eysenck and Eysenck, 1964). The test consists of two sets of questions which are worded simply to be readily comprehensible. The test incorporates a "lie scale," and any patient with a lie score greater than 4 was not included; the 44 patients who provide the material for this study all had lie scores of less than 4. All patients performed the test after completing measurements of $F.E.V._1$, vital capacity, and $P\bar{v}CO_2$. The interview was conducted with the patient isolated, but the technician who performed the tests of lung function was present and she provided a set pattern of explanation and instruction about the test. The results of the inventory were determined as a raw number of extravert, neurotic, and lie score. The raw scores for extraversion (E score) and neuroticism (N score) were standardized for age and occupation, and have been expressed as such.

Results

The correlation between E score and N score with the actual−predicted $P\bar{v}CO_2$ is shown in Figs. 1 and 2. In Fig. 1 there is a significant correlation between the E score and actual−predicted P_{CO_2} ($P>0·001$) in contrast to Fig. 2, which fails to show any significant correlation between the N score and the actual−predicted $P\bar{v}CO_2$ ($0·3>P>0·2$). Both figures are summarized in Fig. 3, which is a histogram of the number of patients with an E or N score greater or less than the mean value of healthy subjects and related to whether or not each patient has an observed $P\bar{v}CO_2$ greater or less than predicted. The random distribution of N scores contrasts with the greater number of E scores above the mean and associated with a lower than predicted $P\bar{v}CO_2$.

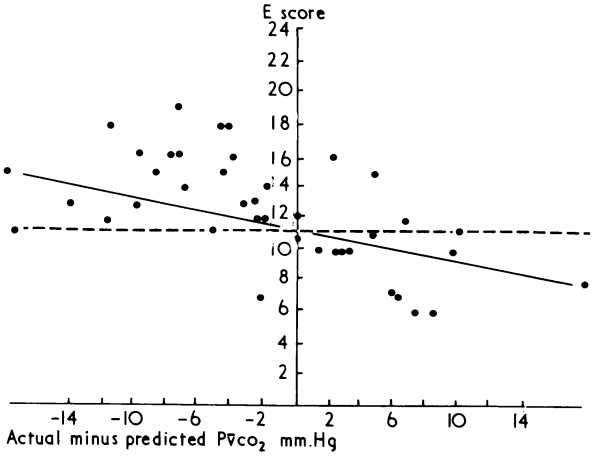

FIG. 1.—Correlation between actual-predicted $P\bar{v}CO_2$ and extravert (E) score.

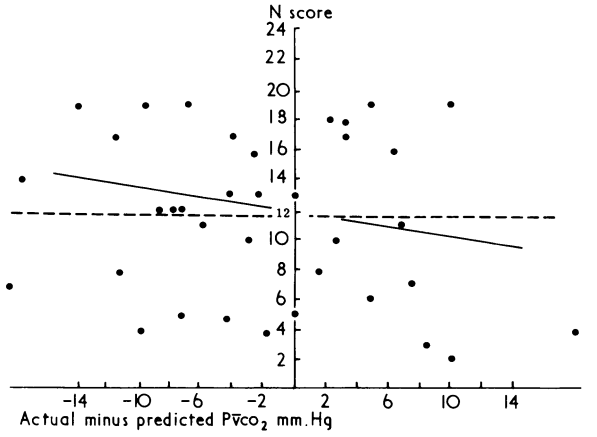

FIG. 2.—Correlation between actual-predicted $P\bar{v}CO_2$ and neurotic (N) score.

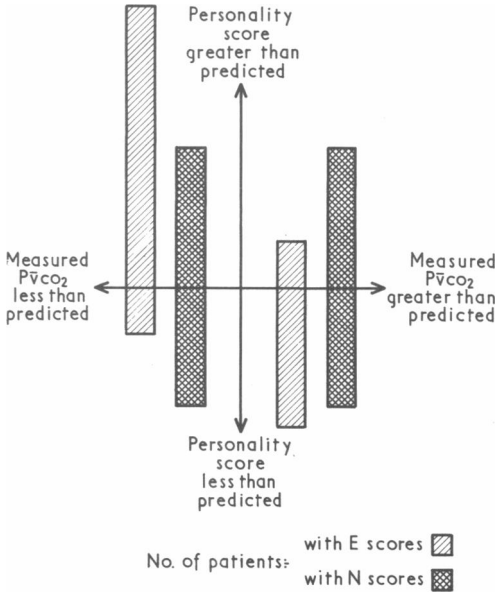

FIG. 3.—Histogram showing number of patients with an E or N score above or below normal and with a $P\bar{v}CO_2$ greater or less than predicted from their $F.E.V._1$.

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