Dr. Bollen stated that we (Robinson and Gray, 1961) serious misquotation; stimulating voltages can play a role in the hyperpolarization rate of the electrode was too high. This is a critique of their results on the grounds that the stimulation of active hyperventilation was satisfied by a decrease in the cerebral arterial/venous oxygen difference of 58 per cent.

Gibbs and Lennox (1942) showed a better correlation between the hyperpolarization and the decrease in cerebral blood flow. The work of Kety and Schmidt (1946) quoting them is perhaps wise to understand the basic functional principles of the apparatus they have used.

Dr. Bollen has commented adversely on our observations of the effects of amyl nitrite and concentrated ammonia vapour and 100 per cent oxygen on the analgesia of passive hyperventilation. Perhaps it would not be inappropriate to reiterate the facts as we published them. We noted that amyl nitrite caused a fall in the analgesia produced by hyperventilation. Dr. Bollen suggests that the cerebral vasodilation produced by the amyl nitrite should have lowered the Pco 2 of the brain and therefore enhanced the analgesia. This is precisely what we did observe, as a more careful examination of our paper would have shown.

On the basis of unpublished observations, Dr. Bollen states that amyl nitrite and concentrated ammonia cannot act by reticular stimulation as this would produce activation of the resting electroencephalogram, which he did not observe. As I have previously explained the e.g. were monitored continuously. Slow waves were produced in eleven out of twenty subjects but no other sequence or change was produced. However, many other factors can be responsible for this appearance; alteration in central venous pressure and blood sugar levels are two well-known examples. As it was not possible to monitor every parameter, it was considered that these observations were of insufficient worth for publication.

Dr. Bollen cites the work of Lennox, Gibbs and Gibbons (1938), who postulated that the vasoconstriction following hyperventilation was a homeostatic mechanism to maintain the carbon dioxide tension of the brain; perhaps he may be interested to learn that later work by the same authors (Gibbs et al., 1942; Nims, Gibbs and Lennox, 1942) showed a better correlation of e.g. patterns with lowered Pco 2, in the internal jugular vein, rather than with lowered Po 2. This is of no help to Dr. Bollen’s hypothesis of cerebral hypoxia.

The author of your review makes some play with the work of Kety and Schmidt (1946), quoting them as showing there was a decline in cerebral blood flow to 65 per cent of the control level and an increase in the cerebral arterial/venous oxygen difference of 58 per cent. A more careful perusal of this most detailed work reveals that during passive hyperventilation the oxygen consumption remained the same, yet during active hyperventilation there was a mean increase in oxygen uptake by the brain of 15 per cent. It is inconsistent, therefore, to suggest that cerebral hypoxia can have occurred because no decrease in cerebral consumption could be demonstrated and the increased oxygen demand of the brain during the intense mental activity of active hyperventilation was satisfied by a large increase in oxygen uptake.

In discussing the work of Sugioka and Davies (1960), Dr. Bollen stated that we (Robinson and Gray, 1961) criticized their results on the grounds that the stimulation rate of the electrode was too high. This is a serious misquotation; stimulating voltages can play no part in the action of the oxygen electrode. We did state that we considered that the rate of application of the polarizing voltage was too rapid and would have led to a high consumption of oxygen at the electrode. If one is going to use reasoned arguments based upon the worth of the experiments of others, it is perhaps wise to understand the basic functional principles of the apparatus they have used.

In our experiments the symptoms of hypoxia, such as are seen on exposure to altitude, were absent. As Dr. Bollen suggests that the lack of symptoms was due to cerebral vasoconstriction produced by hyperventilation instead of the dilatation by hypoxia. This is a spurious argument. Surely it is well known that exposure to lowered barometric pressures induces hyperventilation and a lowered arterial Pco 2; consequently cerebral vasoconstriction is common to both conditions.

On somewhat broader principles there have been several reports of patients being subjected to deliberate hyperventilation for periods of weeks (Avery, Mösch and Benson, 1956; Clarkson and Robinson, 1962), yet there have never been any reports of the signs of cerebral damage which might reasonably have been expected to accrue if cerebral hypoxia was a feature of the management of such patients.

The only scientific approach to the problems presented by passive hyperventilation is a biochemical one. Hyperventilation initially produces changes in pH, Pco 2, and later in the metabolic component of the acid/base balance. There is no doubt that during hyperventilation, with its concomitant lowered arterial Pco 2, glycolysis proceeds to the production of fixed acids, particularly pyruvic and lactic acid. This is the so-called metabolic acidosis of hyperventilation.

To enter the tricarboxylic acid cycle, pyruvic acid must be changed via acetylcoenzyme A to oxaloacetic acid. If the cycle is to continue, oxaloacetic acid must...
be continually replaced and one of the proven ways of producing it is the Wood-Werkman reaction (1943), i.e.

$$\text{Phosphoenol pyruvate} + CO_2 \rightarrow \text{oxaloacetic acid.}$$

In the hyperventilated state, there is a marked tissue gradient of Pco₂ from the cells to the vessels and this greatly reduces the amount of carbon dioxide present in the body pool available for such synthetic reactions. Furthermore, Eichenholz et al. (1962) gave clinical proof of this reaction when they showed that the production of fixed acids during passive hyperventilation was dependent on the reduction of Pco₂ and not on the e.e.g.

Cerebral metabolism is almost entirely dependent on glucose and at least 75 per cent of the energy available to the brain is produced by the tricarboxylic acid cycle, whereas glycolysis alone can give less than 10 per cent of the available energy. It must be obvious, therefore, that passive hyperventilation without cerebral hypoxia reduces the metabolism of the brain, but then, so does every anaesthetic agent.

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REFERENCES


Sir,—I was interested in Dr. A. R. Bollen's review of the electroencephalogram and hyperventilation (Bollen, 1962). There are, however, one or two important facts on which he does not comment. Perhaps the most significant of these is that Kety and Schmidt (1946) showed that, despite the lowering of cerebral oxygen tension attendant upon hyperventilation, there was no alteration in the uptake of oxygen. This finding has been quoted by Robinson and Gray (1961) as evidence against any cerebral hypoxia occurring during hyperventilation. I feel that it is important to realize that this conclusion does not necessarily follow because it is a well-accepted physiological finding that alkalosis increases the excitability of all conducting tissue in the body—for example, this increased excitability of the brain is used by neurologists to activate the e.e.g. during investigations into epilepsy. If there is an increase in cerebral excitability there may also be an increase in the demands for oxygen which may not be met where there is cerebral vasocostriction.

It has also been suggested (Price, 1962) that since cerebral hypoxia causes considerable vasodilatation, the vasocostriction produced by hyperventilation will not cause cerebral hypoxia as the hypoxia would restore the cerebral blood flow to an adequate level. This argument again is unsound in that some cerebral hypoxia must be present before the compensatory mechanism comes into play. Any cerebral hypoxia, however, would be self-limiting.

The critical experiments, to my mind, would seem to be the effects of breathing 100 per cent oxygen on the analgesia produced by hyperventilation since high oxygen can only cause increased vasocostriction. The results of my rather inadequate experiments (Clutton-Brock, 1957) seemed to indicate that oxygen reduced the analgesia. Robinson and Gray (1961) found no effect, but the present study that I used oxygen in the presence of what was probably very mild hyperventilation, though we had not, at that time, the equipment to measure the degree of alkalosis produced. Robinson and Gray were producing severe alkalosis and it may be that high oxygen will only reduce the degree of analgesia in the presence of slight alkalosis. I am sure that these experiments should be repeated, and this we hope to do soon, using a more accurate method of measuring analgesia.

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REFERENCES
