Gas Exchange in Renal Failure

SIR,—In their interesting paper (1 May, p. 244), Drs. M. J. Goggin and A. M. Joekes successfully lay emphasis on an already well-established point—namely that a rise in $Paco_2$ may be accompanied by a rise in serum potassium. In addition, they do well to remind us that respiratory compensation for metabolic acidosis may be abolished under anaesthesia. These are important points well made.

However, I am fearful lest a casual reader of their paper may now think suxamethonium to be exonerated as a potential cause of hyperkalaemia in renal failure. As I believe this matter to be still sub judice, may I make the following observations.

They state that in cases 1a, 4, 5, 6, and 9 the compensation for metabolic acidosis present during spontaneous conscious breathing is to a greater or lesser extent abolished under anaesthesia. However, in case 1a there is no direct evidence of preoperative hyperventilation, and in case 4 there is direct evidence of the absence of preoperative hyperventilation. In case 6 the preoperative $Paco_2$ is within normal limits, the pH may also be, depending on the third decimal place, and the calculated base excess is only marginally below the lower limit of normal. It is interesting, too, that while case 9 exhibited a marked rise in serum potassium level, the rise in $Paco_2$ and the fall in pH were less than those seen in cases 5 and 6, where the serum potassium remained essentially normal.

They state that case 2 was spontaneously overbreathing. The preoperative $Paco_2$ is, however, normal and the mild alkalosis is metabolic in origin, not respiratory.

In three of the eight cases where suxamethonium was employed (cases 1a, 3, and 4) there was a marked rise in serum potassium. The largest rise (1 mEq/l) was seen in case 3. Here it is not associated with any marked change in $Paco_2$, but rather with a small rise in pH. It may well represent an effect due to suxamethonium.

No details of suxamethonium dosages are given, and intraoperative blood samples were drawn at least 30 minutes after induction of anaesthesia (with one exception). In normal man the rise in serum potassium after suxamethonium is probably dose-related. It is maximal at about 7 minutes post-injection and is of the order of 0.55 mEq/l after a 100 mg dose.[1] Thirty minutes after a 40 mg dose, however, one would not expect to detect this rise.

The brief report by Powell and Golby[2] of a study in rats strongly suggests that potassium release following suxamethonium is highly abnormal in acute renal failure. A fuller report of this study is in press.

It has been shown[3] in burned patients that the rise in serum potassium after suxamethonium is exacerbated by any concomitant acute rise in $Paco_2$. In contrast, when suxamethonium was not employed no rise in potassium levels were seen.

In conclusion, it seems that the relative importance of the administration of suxamethonium and of changes in acid/base status is not yet settled. It is likely that both, on occasions, are significant factors in the production of hyperkalaemia, and, they may well be additive.—I am, etc.,

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Hiccup

SIR,—Your leading article entitled "Hiccup" (1 May, p. 234) reminds me of an unpleasant personal experience during a holiday in France.

I fell ill with symptoms of indigestion and persistent hiccup. After hours of this exhausting trouble I saw a doctor who applied a spray of local anaesthetic into my throat, the hiccup stopped immediately to recur after half an hour. The same effect after a second application with a stronger dose. Questioned by the doctor whether I would mind taking some homoeopathic drugs my answer was, I don't mind anything; I only want to get rid of this hiccup. I had to take one small pill of copper and one of coccolus alternatively every half an hour. After only 45 minutes the serious phenomenon stopped for good.

I remembered the words of Hamlet: "There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy."—I am, etc.,

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SIR,—Reading your highly scientific leading article (1 May, p. 234) entitled "Hiccup" I was somewhat surprised to find no reference to the relationship between hiccup and sneezing, described, I believe, by Hippocrates.

Using a very small amount of much maligned tobacco in the form of snuff provokes sneezing, bringing trivial hiccup to a speedy end.—I am, etc.,

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Human Growth Hormone

SIR,—In your leading article on the structure of human growth hormone (1 May, p. 236) you conclude that it is unlikely to be made synthetically for human therapy for a long time to come. The structural evidence on which this conclusion was based was published between May 1966[1] and December 1970.[2]

Present progress in peptide hormone chemistry is so rapid that records of the structure already need to be revised and your conclusion to be reviewed. This remarkable rate of advance is undoubtedly owing to the availability of automatic techniques. In addition to the methods for amino-acid analysis and peptide synthesis to which you refer automatic sequence determination is now practicable.[3,4] Niall[5] has used it to re-examine the amino-terminal region of human growth hormone and found that a sequence of 15 amino-acids was misplaced in the structure reported by Li *et al.* Niall's revised structure shows that the sequence homology between human growth hormone and human placental lactogen is much closer than previously thought. At least two other important conclusions can be drawn.

(1) The work clearly illustrates some of the drawbacks of solid state synthesis discussed by Bayer *et al.*[6] and Rudinger.[7] Li and Yamashiro had no reason to be surprised that their synthetic product had only 10% of the biological activity of the purest natural growth hormone, because it was impossible to know to what extent it might be contaminated with a host of error peptides. Each of these might perhaps differ from the intended sequence only by the absence of a single residue and be impossible to remove at the end of the synthesis.

(2) The very fact that material of unknown chemical purity synthesized according to the incorrect sequence had significant biological activity shows that structural integrity of the total growth hormone sequence cannot be required for it to exert its effect. This was pointed out by Niall and underlined editorially.[8]

The results of attempts to synthesize active fragments and analogues of human growth hormone are awaited with the greatest interest and may shorten the requirement for growth hormone prepared from human pituitaries to which you refer.—I am, etc.,

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6 Bayer, E., *et al.*, *Journal of the American Chemical Society*, 1970, **92**, 1735.
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Jejunal pH and Folic Acid

SIR,—The criticism levelled by Dr. W. F. Doe and others (20 March, p. 669) at our paper on the "Effect of Intraluminal pH on th absorption of Pteroylmonoglutamic Acid" (16 January, p. 148) prompts us to clarify certain points raised in their letter.

At no stage was it suggested that alteration in the intraluminal pH is the sole governing factor in folate deficiency states. Experimentally in the rat everted sac folic acid transport is pH dependent, such that a small change in pH from 6·5 to 7·0 will reduce folic acid transport by more than 50%.[1] In certain chronic epileptics who had developed megaloblastic anaemia on anticonvulsants, intraluminal conditions conducive to folate malabsorption have been detected. Similar alkaline conditions have been found in some patients with adult coeliac disease who also had low serum folates. Since folate deficiency in man is complex in aetiology the finding of an alkaline jejunal pH represents only one possible contributory factor, and the effect of alkalinity could be overcome by high dietary intake or adequate therapeutic doses of folic acid.

Our paper contains no reference to the mechanism by which phenytoin produced an alkaline intrajejunal state. We favour a metabolic mechanism for the phenomenon, since only at the end of a 10-day period