Gas Exchange in Renal Failure

SIR,—In their interesting paper (1 May, p. 244), Drs. M. J. Goggin and A. M. Joeckes 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 Golby² 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 shown³ 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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- ¹ Weintraub, H. D., Heisterkamp, D. V., and Cooperman, L. H., *British Journal of Anaesthesia*, 1969, **41**, 1048.
- ² Powell, J. N., and Golby, M. G. S., *British Journal of Anaesthesia*, 1970, **42**, 804.
- ³ Gronert, G. A., Dotin, L. N., Ritchey, C. R., and Mason, A. D., *Anaesthesia and Analgesia* . . . *Current Researches*, 1969, **48**, 958.

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.,

W. JONAS

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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 1966¹ 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} Niall⁵ 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 impor-

tant 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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- ¹ Li, C. H., Liu, W. K., and Dixon, J. S., *Journal of the American Chemical Society*, 1966, **88**, 2050.
- ² Li, C. H., and Yamashiro, D., *Journal of the American Chemical Society*, 1970, **92**, 7608.
- ³ Edman, P., and Begg, G., *European Journal of Biochemistry*, 1967, **1**, 80.
- ⁴ Niall, H. D., and Potts, J. T., in *Proceedings of the First American Peptide Symposium*, ed. B. Weinstein, New York, Dekker, 1969.
- ⁵ Niall, H. D., *Nature New Biology*, 1971, **230**, 90.
- ⁶ Bayer, E., *et al.*, *Journal of the American Chemical Society*, 1970, **92**, 1735.
- ⁷ Rudinger, J., in *Radioimmunoassay Methods*, ed. K. E. Kirkham, and W. M. Hunter, Churchill Livingstone, 1971.
- ⁸ *Nature New Biology*, 1971, **230**, 65.

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 the 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 anti-convulsants, 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

of Garoin (phenytoin 100 mg and phenobarbitone 50 mg) treatment did a normal control subject exhibit impaired folate absorption. We agree that the effect of sodium bicarbonate is not strictly comparable to that of phenytoin, but suggested only that the impaired absorption produced by alkalization with sodium bicarbonate mimics the alkalization and malabsorption produced by long-term phenytoin treatment, the mechanism of which remains obscure.

The failure to consider the effect of pH on the availability of pteroylmonoglutamic acid has led to conclusions which merit reconsideration. Thus Hepner² measured folic acid transport across the rat jejunum from solutions of folic acid, folic acid plus phenytoin, and folic acid plus methotrexate respectively. At no stage was the effect of pH considered, nor was the intraluminal pH measured. The impairment of absorption of folic acid by phenytoin and methotrexate, both of which give alkaline solutions, could reflect the direct effect of pH. Similarly, when considering the uptake of 5-methyltetrahydrofolic acid by lymphocytes, Das and Hoffbrand³ showed 50% inhibition of absorption by methotrexate. Solution of methotrexate at this concentration (10^{-3} M approx) can only be obtained at an alkaline pH, and again the impaired uptake noted might well have been due to a pH effect. Das and Hoffbrand concluded that the uptake of folic acid by lymphocytes was an active process based on inhibition by methotrexate, temperature effects with a temperature coefficient of about 2, and linear increase in uptake until saturation occurs. Active transport would be better indicated by a temperature coefficient greater than 3,⁴ inhibition by methotrexate is invalid for reasons already stated, and saturation phenomena are not necessarily characteristic of active transport.⁵⁻⁷ Hence the uptake of 5-methyltetrahydrofolic acid by active transport is not proven. Uptake of folic acid by blood platelets has been shown to be a passive process.³ In conclusion, we stress that in any study of the mechanism of folate absorption, due consideration must be paid to the effects of pH.—We are, etc.,

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- 1 Smith, M. E., Matty, A. J., and Blair, J. A., *Biochimica et Biophysica Acta*, 1970, 219, 37.
- 2 Hepner, G. W., *British Journal of Haematology*, 1969, 16, 241.
- 3 Das, K. C., and Hoffbrand, A. V., *British Journal of Haematology*, 1970, 19, 203.
- 4 Davson, H., and Danielli, J. F., *Permeability of Natural Membranes*. 2nd. edn. London, Cambridge University Press, 1952.
- 5 Newey, H., and Smyth, D. H., in *Biological Basis of Medicine*, ed. E. E. Bittar and N. Bittar. Volume 5, p. 360. New York, Academic Press, 1969.
- 6 Wilson, T. H., *Intestinal Absorption*, p. 54, 83. Philadelphia, Saunders, 1962.
- 7 Blair, J. A., and Matty, A. J., unpublished.
- 8 Gaut, Z. N., Solomon, H. M., and Baugh, C. M., *Biochimica et Biophysica Acta*, 1970, 215, 194.

Deaths from Dental Anaesthesia

SIR,—Under the above heading (3 April, p. 59) you report Sir Keith Joseph's reply to a question asked in Parliament.

With respect, I would point out that his reply was misleading. The questioner asked how many patients "of dentists practising intravenous anaesthesia" had died as a re-

sult of it during the past five years. Sir Keith replied that, of 32 deaths with dental anaesthetics during this period in 11 there was mention of methohexitone or similar intravenous anaesthetic agent. This might well give the impression that in these 11 fatalities anaesthesia was in the hands of dentists giving their own intravenous anaesthetics, and that the intermittent injection method was the cause of death. In actual fact, in most of the 11 fatalities the anaesthetics were given by consultant anaesthetists, and the intravenous agent was used only for induction.

Sir Keith (himself misled apparently) went on to say that he would shortly be making regulations to put a stop to the practice of the dentist giving his own anaesthetics. Some years ago I pointed out¹ that this practice was not a cause of deaths and to stop it would not improve the mortality; the real danger was something totally different that had been overlooked.

I have recently produced² further evidence substantiating this view.—I am, etc.,

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- 1 Bourne, J. G., *Lancet*, 1966, 1, 879
- 2 Bourne, J. G., *Anaesthesia*, 1970, 25, 473

In a further answer on 10 May Sir KEITH JOSEPH said that of the 11 registrations of death referred to in his reply on 16 March (see *B.M.J.*, 3 April, p. 59) the anaesthetic involving the use of methohexitone or similar anaesthetic agent was in two cases administered by the operating dental surgeon and in nine by an anaesthetist.—Ed., *B.M.J.*

Viral Hepatitis and the E.S.R.

SIR,—It has been established experimentally that there are two types of viral hepatitis: the short incubation period type, and the long incubation period type, in which the hepatitis-associated antigen (H.A.A.) is found.¹ In sporadic viral hepatitis it is not usually possible to distinguish these clinically.²

In 1969 I noted that some patients suffering from viral hepatitis had a normal erythrocyte sedimentation rate (E.S.R.) throughout their illness: others had, on admission, a high E.S.R., which gradually became normal. During 1970, 65 patients over the age of 12 years were studied. Five children under 12 years old of both sexes who were antigen-negative and had an E.S.R. ranging from 45-68 mm/1 hr. were excluded from the statistical analysis. The first E.S.R. result, obtained as soon after admission as possible, was used. This was usually within 14 days of the onset of the first symptoms (range 2-36 days). Blood for the double-diffusion antigen test was taken at the same time. Two standards were used for the analysis, as there is no general agreement as to what is normal. Dacie and Lewis consider that the maximum should not exceed 5 mm/1 hr. for males and 7 mm/1 hr. for females.³ Other authorities consider it should be 15 mm/1 hr. for both sexes. These figures take into account the variations due to menstruation.

Table I shows the composition of the series in terms of antigen result, sex and age range.

TABLE I

Antigen	Males	Females	Age Range	Total
Positive	20	7	19-47	27
Negative	21	17	12-64	38
Totals	41	24	12-64	65

There were no patients with the H.A.A. under 19 years or over 38 years of age. Apart from this the age incidence in both groups was similar. About two-thirds of the patients were between 18 and 19 years old. This was because most of them came from districts having a large floating population of young people living in hostels and "bed-sitters". The relationship between E.S.R. and the antigen test result is shown in Tables II and III.

TABLE II

Normal: 5 mm/1 hr. males; 7 mm/1 hr. females			
H.A.A.	Normal E.S.R.	High E.S.R.	
Positive	16	11	
Negative	5	33	

$$p = < 0.0005 (\chi^2 \text{ Test})$$

TABLE III

Normal: <15 mm/1 hr.			
H.A.A.	Normal E.S.R.	High E.S.R.	
Positive	21	6	
Negative	11	27	

$$p = < 0.0005 (\chi^2 \text{ Test})$$

I am grateful to Dr. A. J. Zuckerman, of the London School of Hygiene, for analysing the above results by computer, using the 2×2 , χ^2 test. With either standard of normality for the E.S.R. the results are highly significant. In other words, a high E.S.R. at the onset of symptoms of viral hepatitis is likely to be found in patients who are antigen-negative and a normal E.S.R. in antigen-positive ones. There were no antigen-positive patients with an E.S.R. of over 23 mm/1 hr., except an Algerian male who had an E.S.R. of 40 mm/1 hr. Blumberg *et al.* found the H.A.A. rarely in North American and European sera but commonly (1-20%) in sera from tropical sources.⁴ It is therefore quite possible that this patient was suffering from a type of hepatitis unassociated with the antigen, although a carrier of it. This case emphasizes the importance of being aware that the presence of the H.A.A. is not always diagnostic of one of the types of viral hepatitis or other causes of jaundice, particularly in patients who come from tropical countries. Two antigen-positive male patients who had a high E.S.R. had been ill for several months; this may indicate that they had developed chronic aggressive hepatitis. To support this view, two similar patients admitted this year were proved to have this condition by needle biopsy. A female antigen-positive patient, who was a drug addict, and a male antigen-positive patient with an infected skin condition were both found to have a high E.S.R. It can therefore be concluded that