They are seen in a large number of different conditions, but are particularly common in hypertensive retinopathy, and may occur in large numbers in certain of the collagen diseases. In both these groups of conditions fibrinoid necrosis of the arterioles is probably the essential lesion.

We believe this is the first report of a retinopathy associated with diffuse fibrosing alveolitis, a retinopathy similar to those seen in certain of the collagen diseases.

ACKNOWLEDGEMENT

We are indebted to Dr. Kenneth Perry, Physician to The London Hospital, for permitting us to describe this case.

REFERENCE

SCADDING, J. G. (1964). *Brit. med. J.*, **2**, 686, 941.

PAST, PRESENT AND FUTURE FIGHT AGAINST METHANOL BLINDNESS AND DEATH

OLUF RÖE

(*From the Eye Dept., Namdal Hospital, Namsos, Norway*)

A STUDY of 82 cases of methanol poisoning during the last World War showed that the development of blindness was closely related to severe acidosis and not to the amount of methanol consumed.[15, 16] This relationship was most clearly seen in cases when severe acidosis developed after admission to hospital.

The reason why this study was done was the discrepancy between the results of clinical and experimental investigations on the effect of alkali treatment. In 1920 Harrop and Benedict[5] and Isaacs[7] reported good results in clinical cases by this treatment. Experiments on animals during the following years gave strong arguments against bicarbonate treatment.[6, 10] It seems as if the authors of medical textbooks paid more attention to experimental than to clinical observations, some of them pointing out that much reliance should not be placed upon the bicarbonate treatment ([16], p. 117). It is not astonishing that doctors having consulted the recent medical literature were afraid of using bicarbonate when the first war-time cases of the poisoning appeared. Consequently most of these patients died. Later on many patients were given bicarbonate in too small amounts with the result that those who survived, suffered from permanent blindness. Still later we learned to use more adequate doses of bicarbonate which was found extremely effective when quickly administered by intravenous injection. But even this treatment could not save the patient's life when respiratory paralysis had developed before start of treatment ([16], p. 134).

The amount of sodium bicarbonate required may be read from Van Slyke's line chart (Fig. 1).

We can here easily see that a patient weighing 70 kgms. and with a blood bicarbonate of 8 m. Eq. per litre should be given

70 gms. of sodium bicarbonate, or about 1½ litres of a 5 per cent. solution. Since the maximum quantity of fluid given in a single injection is 2 litres,[8] it is obvious that an isotonic or 1·3 per cent. solution is not suitable in the treatment of severe methanol acidosis.

In order to show you an example of the effectiveness of a quickly performed bicarbonate treatment I should like to refer shortly to a patient treated in 1943 ([15], case 14, p. 580). The

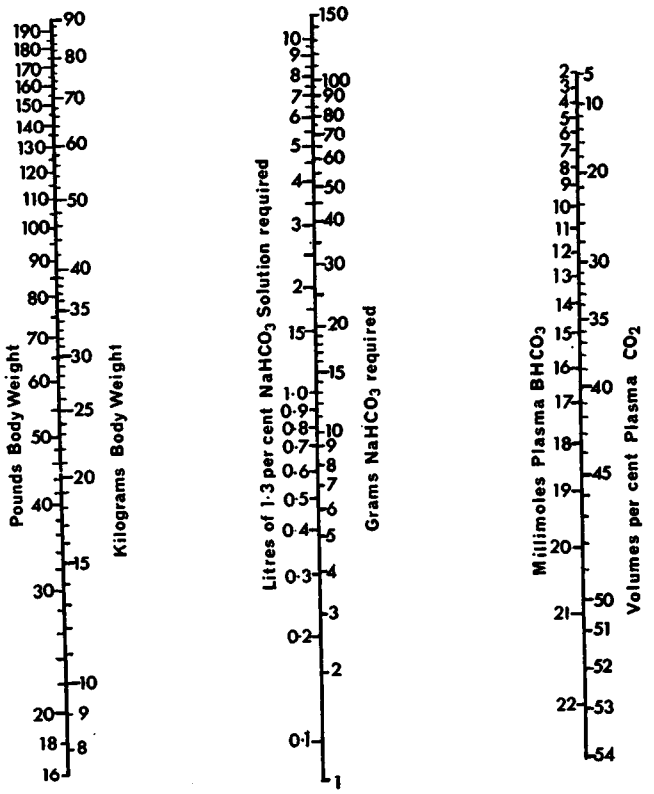

FIG. 1.

Van Slyke's line chart for estimating the amount of sodium bicarbonate required in conditions of alkali deficit to raise the CO_2 content of the plasma to 60 volumes per cent. or the $BHCO_3$ content to 25 millimoles per litre. A straight line cutting the scales for body weight and plasma CO_2 or $BHCO_3$ content will cut the middle scale at a point indicating the bicarbonate administration required.[23]

symptoms were: coma, dyspnœa, cyanosis and rubœsis of the skin, general rigidity of the limbs and some clonic contractions. The pupils were dilated, 6 mm., reacting very feebly to light. The blood bicarbonate was 8 m. Eq./L., lactic acid 170 mg. per cent. and formic acid 3·5 mg. per cent. Twenty-five minutes after admission he was given 450 ml. of a 5 per cent. solution of sodium bicarbonate intravenously and in addition about 30 gm. bicarbonate through a stomach tube. Ophthalmological examination 5 hours later showed normal pupils, 3·5 mm., reacting quickly to light. Vision 6/6 in both eyes.

The additional use of ethanol has been recommended since 1943 because it has been demonstrated that this alcohol had an inhibitory effect on the development of methanol acidosis.[15] The hypothesis was put forward that this effect was due to inhibition of methanol oxidation. It was soon demonstrated by many experiments, primarily by those carried out by Zatman[26] and Bartlett,[1] that ethanol inhibits methanol oxidation very markedly. In spite of these findings it was advised strongly against ethanol therapy in publications from 1952[14] and 1955.[12] In many animal experiments the authors had found that ethanol *increased* the toxicity of methanol. The history of this treatment thus has some points of resemblance with that of alkali treatment. It will be remembered that bad results had been achieved by bicarbonate treatment of poisoned animals.

It has been pointed out repeatedly that ethanol should be given as a supplement to bicarbonate treatment ([15], p. 602; [16], p. 122; and [17], p. 406). Inhibition of methanol oxidation while the patient is comatose from severe acidosis, cannot result in a speedy improvement of the patient's state. This can be achieved only by rapid correction of the acidosis.

During the last decade a third method has been recommended in the treatment of methanol poisoning, i.e. the dialysis treatment. According to Schreiner[20] this treatment is effective in acute poisonings provided the poison in question fulfils four requirements: (*a*) diffusability, (*b*) distribution in equilibrium with plasma water, (*c*) a time-dose-cytotoxic relationship and (*d*) a dialysance significantly additive to metabolism and excretion.

In human methanol poisoning the severity of symptoms is not related to blood methanol concentration or to duration of body exposure to the poison.[15, 16, 18, 19] The post-mortem blood methanol content in 23 fatal cases varied between 0·51 and 2·74 g. per litre.[16] In two other fatal cases the blood methanol on admission was 0·2 and 0·3 g. per litre.[4]

Marc-Aurele and Schreiner[11] have shown that methanol is a readily dialysable substance, and that early dialysis in methanol-poisoned dogs is successful. While in animals a close relationship exists between amount of methanol given and severity of symptoms, this is not so in human methanol poisoning. Here the all important nosological factor is the severe acidosis. From a theoretical point of view there should therefore be no reason to expect good results from dialysis in human methanol intoxication. Nevertheless it has been used and strongly recommended in some countries.[4, 21, 22, 25]

I now intend to give you an impression of the present treatment of this poisoning by shortly referring to 11 patients, of whom 9 were treated by dialysis. In all cases some bicarbonate and/or ethanol was given in addition, but mostly in inadequate quantities.

The cases A and B were reported from Sweden in 1963.[2] In the first case the patient was comatose on admission and was later transferred to an intensive care unit because of respiratory and cardiac arrest. The second patient, who was *not* comatose, had severe abdominal pains, Kussmaul's respiration and amaurosis. When his condition later deteriorated he was transferred too, and only *during* the transport did respiratory and cardiac paralysis occur. Needless to say that such a transfer means a disastrous delay of treatment. The extremely low blood pH 6 hours after admission and the slight rise of blood bicarbonate during 12 hours demonstrate a very inadequate treatment of the acidosis.

The next three cases (C, D, E) were described from U.S.A. in 1960.[22] These patients were given too much bicarbonate but nevertheless there was too slow correction of the acidosis in the first phase of treatment as the slope of the curves show. The first two patients were not comatose on admission, the first being amaurotic the second amblyopic. Both of them went

blind. It is my experience that patients in whom some vision is still present at the start of treatment—or some reaction of the pupils to light—will regain vision very soon by quick correction of the acidosis. The third patient died from tetanic seizures undoubtedly provoked by severe alkalosis. Peritoneal dialysis, which had started respectively 6, 10 and 8 hours after admission, cannot have had any influence on the course of the poisoning.

From Denmark case F was reported in 1961.[25] This female patient got no treatment before two hours after admission when respiratory paralysis developed and persisted in spite of intubation and artificial respiration. It is interesting that

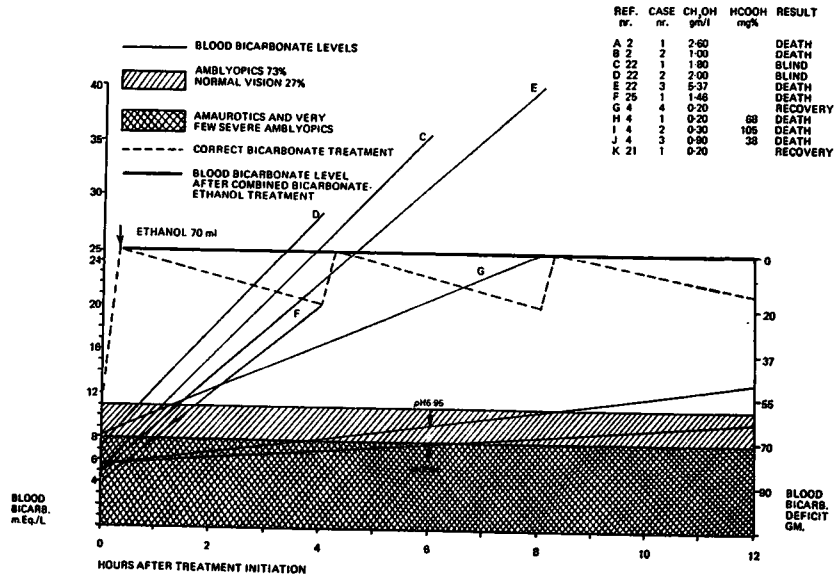

FIG. 2.

The left scale represents blood bicarbonate in m. Eq. per litre and the right one the corresponding bicarbonate deficit or the amount of sodium bicarbonate required for complete correction of the acidosis. By decreasing blood bicarbonate vision begins to fail in the lightly shadowed area and is mostly totally lost in the darkly shadowed area, according to earlier investigations.[16] The broken line indicates the rise of blood bicarbonate by correct initial treatment and later treatments for recurrences of acidosis. The thick horizontal line indicates blood bicarbonate level when recurrence of acidosis is prevented by ethanol. The other lines represent the rise of the blood bicarbonate level in those of the cases in which sufficient data were available from the records (cases A through G). Details on these and other cases in the text.

repeated recording of the electroencephalograms showed at first but slight and later no activity. No wonder that coma persisted in spite of bicarbonate treatment. The course of this case is in good correspondence with our experience during the war. It is not possible to save a patient when respiratory paralysis has developed ([16], p. 134). Since this paralysis in cases of methanol poisoning only occurs when acidosis is extremely severe it can be prevented by early bicarbonate administration. Demodialysis started 12 hours after admission, which, in the author's opinion possibly determined the fate of the patient. Actually, her fate was sealed already when the respiration stopped.

The patient G—a woman—was the only surviving of four, all treated by hemodialysis in the same hospital and reported from Sweden in 1963.[4] This patient was first admitted to the hospital of her home town, her symptoms being Kussmaul's respiration and amaurosis, but she was not comatose. An intravenous drip infusion of a bicarbonate solution was started and continued during the transport to a dialysis clinic of another town. On arrival she was semicomatose, blood bicarbonate was 8·3 m. Eq. per litre and blood pH 7·09. Since coma soon developed more bicarbonate was given before hemodialysis had begun and was continued during this 8-hour procedure. All together 110 g. sodium bicarbonate was given, resulting in complete correction of acidosis and return of vision. The dialysis fluid contained only 4 g. methanol and 13 g. formic acid, but still the favourable result was credited to the dialysis and not to the bicarbonate treatment. The three other patients (H, I and J) died in spite of dialysis treatment. They were not given adequate amounts of bicarbonate.

The last case (K) was recorded from U.S.A. in 1961.[21] This female patient was semicomatose with dilated pupils reacting feebly to light. Serum carbon dioxide content was 5·1 m. Eq. per litre and blood methanol about 0·2 g. per litre. Besides a very small amount of bicarbonate—7·4 g.—she was given 60 ml. of ethanol in a litre of distilled water rapidly injected intravenously, and sustaining doses of 6 ml. per hour were given. In my opinion this ethanol treatment was in all respects correctly performed ([16], p. 122). Since ethanol has a strong,

competitive inhibitory effect on methanol oxidation,[1, 26] and the blood methanol content in this case was very low, the ethanol treatment was certainly able to inhibit methanol oxidation completely resulting in recovery. In analogy to this case I have seen a man who cured himself by drinking considerable amounts of ethanol after having developed severe acidosis and amblyopia ([15], p. 577, case 10). In the present case it was assumed that hemodialysis had saved the patient's life and sight. I cannot agree with this assumption. The fact that the patient remained semicomatose for 2½ hours must be traced to the very low dose of bicarbonate given. It was only one-tenth of the amount required for complete correction of the acidosis.

Methanol poisoning is a global problem against which a campaign should be started. Most doctors are unfamiliar with the diagnosis and treatment of this poisoning. A quick diagnosis is the key to correct therapy. Information should therefore be distributed from the Health Department of every country to all doctors—in and outside hospital. The well-known clinical symptoms of severe acidosis plus amblyopia or amaurosis, dilated, feebly reacting or fixed pupils, is a syndrome pathognomonic for this poisoning. A patient presenting this syndrome should without delay be given 1·5 litres of a 5 per cent. solution of sodium bicarbonate intravenously.

If a medical practitioner has no opportunity to give intravenous injection, he should give the best possible emergency treatment with ethanol and bicarbonate—if necessary through a stomach tube—*before* the patient is sent to hospital for further supervision and treatment. This supervision is necessary during four days if very much methanol has been consumed. Once I saw a hospitalized patient who had been correctly treated for three days, went blind on the fourth day when he developed acidotic coma.

Fifty years ago the doctors using bicarbonate treatment determined the 'alkali reserve' by the method worked out by Van Slyke and Cullen in 1917[9, 24] and the treatment was guided by the blood bicarbonate analysis. Today it seems as if the amount of bicarbonate often is given by chance rather than on the basis of calculations.

During the past 25 years I have advocated the combined bicarbonate-ethanol treatment as the safest and easiest to perform. I feel it is my duty to continue to do so. I therefore appreciate very much having been given the opportunity to read my paper before this great ophthalmological society.

References

[1] Bartlett, G. R. (1950). *Amer. J. Physiol.*, **163**, 619.

[2] Blomberg, R., Cronstedt, J., and Lundberg, S. (1963). *Svenska Läkaretidn.*, **60**, 1937.

[3] Cooper, J. R., and Kini, M. M. (1962). *Biochem. Pharmacol.*, **11**, 405.

[4] Erlanson, P., Fritz, H., Hagstam, K. E., Liljenberg, B., and Tryding, N. (1963). *Svenska Läkaretidn.*, **60**, 3692.

[5] Harrop, G. A. Jr., and Benedict, E. M. (1920). *J. Amer. med. Ass.*, **74**, 25.

[6] Haskell, C. C., Hilleman, S. P., and Gardner, W. G. (1921). *Arch. intern. Med.*, **27**, 71.

[7] Isaacs, R. (1920). *J. Amer. med. Ass.*, **75**, 718.

[8] Kirk, E. (1942). Acidosens Klinikk og Behandling. Copenhagen.

[9] Langfeldt, E. (1936). Lærebok i fysiologisk og medisinsk kjemi. Oslo.

[10] Leo, H. (1925). *Deutsche med. Wschr.*, **51**, 1062.

[11] Marc-Aurele, J., and Schreiner, G. E. (1960). *J. clin. Invest.*, **39**, 802.

[12] Moeschlin, S., and Garson, H. (1955). *Schweitz. med. Wschr.*, **85**, 61.

[13] Pohl, J. (1893). *Arch. für. exper. Path. u. Pharmakol.*, **31**, 281.

[14] Potts, A. M., and Johnson, L. V. (1952). *Amer. J. Ophthal.*, **35**, Part II, 107.

[15] Röe, O. (1943). *Acta med. scand.*, **113**, 558.

[16] ——— (1946). *Acta med. scand.*, **126**, Suppl. 182.

[17] ——— (1948). *Acta ophthal.*, **26**, 169.

[18] ——— (1955). *Pharmacol. Rev.*, **7**, 399.

[19] ——— (1955). *Schweiz. med. Wschr.*, **85**, 813.

[20] Schreiner, G. E. (1958). *A.M.A. Arch. int. Med.*, **102**, 896.

[21] Shinaberger, J. H. (1961). *A.M.A. Arch. int. Med.*, **108**, 937.

[22] Stinebough, B. J. (1960). *A.M.A. Arch. int. Med.*, **105**, 613.

[23] Van Slyke, D. (1934). *New York Acad. Med.*, **10**, 103.

[24] ———, and Cullen (1917). *J. biol. Chem.*, **30**, 289.

[25] Wieth, J. O., and Jörgensen, H. E. (1961). *Dan. med. Bull.*, **8**, 103.

[26] Zatman, L. J. (1946). *Biochem. J.*, **40**, 67.