REFERENCES

Bernhard, H. (1965). *Diabetes*, **14**, 59.
Cerasi, E., and Luft, R. (1967). *Diabetes*, **16**, 615.
Coore, H. G., and Randle, P. J. (1964). In *The Structure and Metabolism of the Pancreatic Islets*, ed. S. E. Brolin, p. 295, Oxford, Pergamon Press.
Fajans, S. S., and Conn, J. W. (1960). *Diabetes*, **9**, 83.
Glueck, C. J., Levy, R. I., and Fredrickson, D. S. (1969). *Diabetes*, **18**, 739.
Grinnell, E. H., Skillman, T. G., Barse, R., and Moller, C. L. (1964). *Current Therapeutic Research*, **6**, 433.
Hoffman, W. S. (1937). *Journal of Biological Chemistry*, **120**, 51.
Idahl, L. A. (1970). In *The Structure and Metabolism of the Pancreatic Islets*. In press.
Loubatières, A. (1944). *Comptes Rendus des Séances de la Société de Biologie et de Ses Filiales*, **138**, 766.
McKendry, J. B. R., and Gfeller, K. F. (1967). *Canadian Medical Association Journal*, **96**, 531.
McMahon, F. G., *et al.* (1962). *Current Therapeutic Research*, **4**, 330.
Montague, W., and Taylor, K. W. (1969). *Biochemistry Journal*, **115**, 257.
Morgan, C. R., and Lazarow, A. (1963). *Diabetes*, **12**, 115.
Rennie, C. S., and Anderson, D. O. (1963). *Canadian Medical Association Journal*, **89**, 669.
Ricketts, H. T., Cherry, R. A., and Kirsteins, L. (1966). *Diabetes*, **15**, 880.
Seltzer, H. S., Allen, E. W., Herron, A. L., and Brennan, M. T. (1967). *Journal of Clinical Investigation*, **46**, 323.
Weaver, J. A. (1966). *Clinical Trials Journal*, **3**, 453.
Williamson, J. R., Lacy, P. E., and Grisham, J. W. (1961). *Diabetes*, **10**, 460.

Acid Production in Diabetic Acidosis; a More Rational Approach to Alkali Replacement

P. Z. ZIMMET,* M.B., M.R.A.C.P. ; P. TAFT,† M.D., F.R.A.C.P. ; G. C. ENNIS,‡ M.B., M.R.A.C.P.
J. SHEATH,§ M.SC., F.A.A.C.B.

British Medical Journal, 1970, **3**, 610-612

Summary: The production of organic acids in severe diabetic acidosis was studied to determine the contribution of various acids and to reassess alkali requirements. In 11 patients the mean total concentration of determined organic acids was 16 mEq/l., while the mean estimated base deficit was 24 mEq/l. Acetoacetic and β-hydroxybutyric acids accounted for 75% of measured organic acid. In 10 patients the mean amount of sodium bicarbonate administered for correction of the acidosis was 185 mEq, while the mean requirement was 394 mEq.

These findings imply that the methods commonly used to determine the base deficit and the alkali requirements in patients with diabetic acidosis may be invalid. The prompt administration of alkali should be limited, and we suggest that the blood *p*H should be restored only to 7·25.

Introduction

In diabetic acidosis, acetoacetic, β-hydroxybutyric, and other acids are formed in the liver more quickly than they can be utilized in the peripheral tissues or excreted by the kidney. The accumulation of these acids in the body fluids has generally been accepted as the cause of the acidosis in this condition (Nabarro, 1965). Concurrently with insulin and fluid therapy, the administration of alkali is a well-recognized emergency measure for correction of the metabolic acidosis (Hudson *et al.*, 1960). One of the main problems associated with alkali therapy is the difficulty in assessing the quantity of alkali to be administered.

The purpose of this study was to determine the contribution of various organic acids to the acidosis of diabetic acidosis and to reassess alkali requirements in the light of our findings.

Patients and Methods

Eleven patients with severe diabetic acidosis were studied. The biochemical criteria for the diagnosis of diabetic acidosis —arterial blood *p*H less than 7·2 and/or plasma bicarbonate less than 10 mEq/l. (Bondy, 1963)—were satisfied in each case. These values, together with initial blood sugar concentrations, are shown in Table I. There were seven females and four males, with an age range from 10 to 74 years. Patients were treated along lines previously suggested (Taft *et al.*, 1968).

Arterial blood samples were obtained from the femoral artery with a heparinized syringe. Samples were taken before treatment and at 4 and 20 hours during treatment. Blood *p*H and P_{CO_2} were measured immediately by the Radiometer microelectrode system. Blood lactic and pyruvic acid levels were measured by an enzymatic method (Boehringer Corporation Ltd.) and free fatty acids by a colorimetric method (Sheath, 1965). Acetoacetic and β-hydroxybutyric acids were separately converted to acetone and measured spectrophotometrically, as the 2-4 dinitrophenylhydrazone of acetone (Paterson *et al.*, 1967). Blood sugar was measured by a ferricyanide procedure.

The severity of the acidosis and the clinical response to the first bicarbonate dose determined the extent of further alkali therapy. In general, patients with an initial arterial *p*H greater than 7·2 received no further alkali, patients with *p*H 7·1 to 7·2 received a further 44 to 88 mEq and those with *p*H less than 7·1 received 110 to 176 mEq. The result of this therapy was checked with another *p*H reading four hours after the start of treatment. No further alkali was required by any of the patients.

Results

Blood Concentrations of Organic Acids on Admission.—The concentrations of the measured organic acids at the time of admission and the mean total of measured organic acid are given in Table II.

Difference between Blood Base Deficit and Measured Organic Acid.—The difference between blood base deficit calculated from the Siggaard Andersen acid-base alignment nomogram (Siggaard Andersen, 1963) and the total measured organic acid is shown in Table III. The mean difference of 8 mEq/l. between the mean blood base deficit and the mean total measured acid represents the discrepancy between excess acid values predicted from the nomogram and those measured.

* Research Fellow.
† Physician-in-Charge.
‡ Former Research Fellow.
§ Research Biochemist.
Ewen Downie Metabolic Unit, Alfred Hospital, Melbourne, Australia 3181.

Difference between Predicted and Actual Alkali Requirements.—The difference between the alkali requirements—calculated from the formula, 0·3 × base deficit (mEq/l.) × body weight (kg.) (Mellemgaard and Astrup, 1960)—and the amount actually given is shown in Table IV. There was a mean difference of 209 mEq between predicted and actual alkali replacement. Despite receiving less alkali than was predicted as necessary for correction of the acidosis, at four hours, five patients had *p*H values within or above the normal range (7·37 to 7·4), and the other five had shown a significant rise toward the normal from their admission *p*H value (Table IV). At 20 hours 9 of the 10 patients had *p*H levels of 7·4 rising to 7·54. All of the alkali was administered between 0 and 4 hours. Data regarding Case 6 have been omitted from Table IV as this patient was too ill for measurement of body weight; therefore alkali requirement could not be accurately calculated for comparison with the alkali administered (440 mEq). She was severely dehydrated, comatose, and shocked, and died four hours after admission.

TABLE I.—*Biochemical Finding on Admission in 11 Patients with Severe Diabetic Acidosis*

Case No.	Age	Sex	Blood Sugar (mg./100ml.)	Arterial *p*H	Actual Plasma Bicarbonate (mEq/l)
1	59	M.	920	7·10	8
2	74	F.	850	7·18	7
3	54	F.	750	7·01	5
4	16	F.	470	6·95	1
5	11	M.	620	7·05	5
6	23	F.	1,110	6·80	1
7	21	F.	400	7·21	7
8	28	F.	370	7·19	2
9	10	F.	1,120	7·08	3
10	13	M.	410	7·21	4
11	20	M.	525	7·25	5

TABLE II.—*Blood Levels of Measured Organic Acids at Time of Admission in mEq/l.*

Case No.	Lactic Acid	Pyruvic Acid	Aceto-acetic Acid	β-Hydroxy-butyric Acid	Free Fatty Acids	Total Acid Measured
1	2·6	0·03	6·3	8·3	1·4	19
2	0·9	0·06	5·1	5·8	0·7	13
3	4·0	0·14	4·2	9·6	1·0	19
4	2·2	0·07	2·3	5·9	1·6	12
5	2·5	0·08	4·1	9·1	2·0	18
6	2·4	0·08	6·2	11·7	1·9	23
7	0·9	0·06	4·2	5·6	1·9	12
8	0·9	0·03	3·8	6·9	0·8	12
9	2·2	0·11	3·2	7·9	1·2	15
10	1·3	0·07	6·2	7·3	1·9	17
11	1·4	0·07	3·5	10·4	1·9	17
Mean	1·9	0·07	4·5	8·0	1·4	16

TABLE III.—*Difference between Base Deficit and Total Measured Organic Acid in Individual Patients*

Case No.	*p*H	P_{CO_2} (mm.Hg)	Base Deficit (mEq/l.)	Total Acid Measured (mEq/l.)	Difference (mEq/l.)
1	7·10	11	26	19	7
2	7·18	23	19	13	6
3	7·01	16	28	19	9
4	6·95	10	30	12	18
5	7·05	14	28	18	10
6	6·80	10	>30	23	7
7	7·21	24	17	12	5
8	7·19	12	23	12	11
9	7·08	10	27	15	12
10	7·21	17	20	17	3
11	7·25	19	18	17	1
Mean			24	16	8

TABLE IV.—*Predicted Alkali Requirement Compared with Alkali Actually Given in 10 Patients, and pH Values at 0, 4, and 20 Hours*

Case No.	Body Weight (kg.)	Base Deficit (mEq/l.)	Predicted Alkali Requirement (mEq)	Alkali Actually Given (mEq)	*p*H 0-Hours	*p*H 4-Hours	*p*H 20-Hours
1	61	26	476	264	7·10	7·27	7·49
2	66	19	376	176	7·18	7·42	7·54
3	57	28	479	176	7·01	7·31	7·44
4	62	30	558	264	6·95	7·22	7·33
5	39	28	328	176	7·05	7·29	7·43
6	—	—	—	—	—	—	—
7	65	17	332	132	7·21	7·37	7·40
8	65	23	449	220	7·19	7·40	7·44
9	38	27	308	264	7·08	7·33	7·44
10	48	20	288	88	7·21	7·38	7·45
11	64	18	346	88	7·25	7·44	7·43
Mean			394	185			

Discussion

Accumulation of acetoacetic and β-hydroxybutyric acid has been accepted as the main cause of the acidosis in diabetic ketosis. In the present study acetoacetic and β-hydroxybutyric acid accounted for 75% of the measured organic acids. The combined levels of β-hydroxybutyric and acetoacetic acid in our patients correspond to those reported by other workers (Martin and Wick, 1943; Nabarro, 1965; Watkins *et al.*, 1969). Our experience and that of others (Watkins *et al.*, 1969) is that the contribution of lactic acid to the acidosis is usually small, being 12% of the measured acid in this series. In fact, a small transient rise in blood lactic acid may occur during the initial treatment of patients with diabetic acidosis, and this is when the acidosis is being corrected (Sussman, 1965; Zimmet *et al.*, 1967; Watkins *et al.*, 1969). None of these patients was receiving lactate as alkali. The degree of lactic acid increase, however, was small and the rise transient.

Base deficit is a term introduced by Astrup *et al.* (1960) to characterize the metabolic (or non-respiratory) component of an acid-base disturbance. Acids generated by deranged metabolism are neutralized at the expense of base, and base deficit expresses the amount (in mEq) of acid which has been generated. By definition, the base deficit is normally zero (Astrup *et al.*, 1960). In the clinical situation the base deficit of blood may be calculated from the Siggaard Andersen acid-base alignment nomogram—*p*H, P_{CO_2}, and haemoglobin measurements being used.

There are several possible reasons why the base deficit calculated from the nomogram exceeds measured total acids on the average by 8 mEq/l. (range 1-18) in these 11 patients.

Firstly, acetoacetic, β-hydroxybutyric, and other organic acids are converted to anions during the buffering process and are then excreted by the kidney as anion. Consequently, the fraction excreted would not have been found in the blood even though it played a part in the production of a base deficit.

Secondly, there may have been present other organic acids which contributed to the acidosis but which were not measured in this study. These might include citric acid, α-ketoglutaric acid, or amino-acids. To explain the difference between base deficit and measured acid, a concentration of 1-18 mEq/l. (the range of difference in our patients) of unmeasured acids would have been required. To our knowledge there are no reported studies of the levels of these acids in diabetic acidosis.

Thirdly, because of the renal impairment due to a combination of dehydration, acidosis, diabetic nephropathy, and possibly hypokalaemia, there may have been impaired hydrogen-ion excretion. This would lead to an accumulation of hydrogen ions in the body fluids, which were not present as measurable organic acid.

Finally, the Siggaard Andersen (1963) blood acid-base alignment nomogram is derived from the earlier reported (Siggaard Andersen and Engel, 1960) and subsequently revised *p*H, log P_{CO_2} blood acid-base curve nomogram (Siggaard Andersen, 1962). The curve nomogram was devised from studies in vitro of blood to which acid or alkali had been added and subsequently equilibrated with CO_2 at two known tensions. Argument has been advanced (Brackett *et al.*, 1965; Bunker, 1965) that the titration curve so obtained in vitro differs from that obtained in vivo. In addi-

tion, it is suggested that in-vitro determinations do not take into account the influence of respiratory compensation on *p*H and P_{CO_2}. Thus possibly, though the alignment nomogram accurately reflects the acid-base changes in the in-vitro circumstances of its design, it may not reflect the disturbances induced by diabetic acidosis.

A recommended approach for the calculation of alkali replacement has been the use of the formula 0·3 × blood-base deficit × body weight in kg. (Mellemgaard and Astrup, 1960). This amount corresponds directly to the amount of sodium bicarbonate required to neutralize a non-respiratory disturbance in the extracellular space (Astrup *et al.*, 1960). The use of this formula does not take into account that in the treatment of diabetic acidosis measures such as insulin and fluid administration, which lead to decreased production and increased metabolism of organic acids, are proceeding at the same time and increasing the capability of the body to buffer, utilize, or excrete these acids. The correction of the acidosis in turn probably increases sensitivity to insulin (Hudson *et al.*, 1960; Phear, 1963). All these factors progressively reduce the alkali requirements of the patient in the initial stages of treatment. Moreover, this formula may not be applicable in this situation for another reason. If, as pointed out previously, there is argument regarding the use of the nomogram then the formula (Mellemgaard and Astrup, 1960) suffers the same limitations because of the use of base deficit (derived from the nomogram) in it.

End results

The results of alkali therapy in our patients showed that though only half of the predicted dose was given, and no further alkali was administered after four hours, the *p*H was fully corrected in five patients and partially corrected in the other five. At 20 hours nine of the patients had *p*H levels above 7·4 and the tenth was just below normal (7·33). In fact, in eight of the patients the end-result of treatment was a mild metabolic alkalosis. Addis *et al.* (1964) also reported the development of metabolic alkalosis in treating diabetic acidosis when this formula has been used.

Had dosages predicted from the formula been used the result might have been too rapid a correction, indeed an overcorrection, of the acidosis, thus possibly aggravating the problems of management due to hypokalaemia which already exists in these patients during the initial stage of treatment (Hudson *et al.*, 1960). In addition, with the use of the high doses predicted by the formula, a more severe metabolic alkalosis may result in the later stages of treatment, though there may not be any side-effects associated with this.

The result of treatment in these patients show the limitations of the alkali replacement formula (Mellemgaard and Astrup, 1960) in measuring the needs for alkali therapy in diabetic acidosis. In treating these patients we have learned that it is not necessary to aim for full *p*H correction with alkali therapy. Our approach has been to raise the blood *p*H to 7·25 with alkali and to allow subsequent complete correction to occur with correction of the underlying cause of the acidosis by insulin therapy. An initial dose of 100 to 150 mEq of sodium bicarbonate should be given, depending on the severity, and then repeat *pH* estimation at one to two hours. Further alkali should be given on the basis of this reading, ceasing therapy when blood *p*H has risen above 7·25.

We acknowledge the performance by the department of biochemistry of blood glucose and blood gas analyses, and we are grateful for the interest and advice of Dr. John Owen and Dr. John Mackenzie in the preparation of the manuscript.

References

Addis, G. J., Thomson, W. S. T., and Welch, J. D. (1964). *Lancet*, **2**, 223.
Andersen, O. S. (1962). *Scandinavian Journal of Clinical and Laboratory Investigation*, **14**, 598.
Andersen, O. S. (1963). *Scandinavian Journal of Clinical and Laboratory Investigation*, **15**, Suppl. No. 70, p. 211.
Andersen, O. S., and Engel, K. (1960). *Scandinavian Journal of Clinical and Laboratory Investigation*, **12**, 177.
Astrup, P., Jørgensen, K., Andersen, O. S., and Engel, K. (1960). *Lancet*, **1**, 1035.
Bondy, P. K. (1963). In *Cecil-Loeb Textbook of Medicine*, ed. P. B. Beeson and W. McDermott, 11th ed., p. 1294. Philadelphia, Saunders.
Brackett, N. C., jun., Cohen, J. J., and Schwartz, W. B. (1965). *New England Journal of Medicine*, **272**, 6.
Bunker, J. P. (1965). *Anesthesiology*, **26**, 591.
Hudson, B., Bick, M., and Martin, F. I. R. (1960). *Australian Annals of Medicine*, **9**, 34.
Martin, H. E., and Wick, A. N. (1943). *Journal of Clinical Investigation*, **22**, 235.
Mellemgaard, K., and Astrup, P. (1960). *Scandinavian Journal of Clinical and Laboratory Investigation*, **12**, 187.
Nabarro, J. D. N. (1965). In *On the Nature and Treatment of Diabetes*, ed. B. S. Leibel and G. A. Wrenshall, p. 545. Amsterdam, Excerpta Medica.
Paterson, P., Sheath, J., Taft, P., and Wood, C. (1967). *Lancet*, **1**, 862.
Phear, D. N. (1963). *British Medical Journal*, **2**, 1581.
Sheath, J. (1965). *Australian Journal of Experimental Biology and Medical Science*, **43**, 563.
Sussman, K. E. (1965). In *On the Nature and Treatment of Diabetes*, ed. B. S. Leibel and G. A. Wrenshall, p. 559. Amsterdam, Excerpta Medica.
Taft, P., Stockigt, J. R., Harrison, J. W., and Cameron, D. P. (1968). *Medical Journal of Australia*, **2**, 825.
Watkins, P. J., Smith, J. S., Fitzgerald, M. G., and Malins, J. M. (1969). *British Medical Journal*, **1**, 744.
Zimmet, P. Z., Taft, H. P., Ennis, G. C., and Sheath, J. (1967). Unpublished data.

Foot Skin Ischaemia in Atherosclerotic Peripheral Vascular Disease

A. J. McEWAN,* M.B., F.R.C.S., F.R.C.S.GLASG. ; C. G. STALKER,* M.B., F.R.C.S.ED., F.R.C.S.GLASG.
I. McA. LEDINGHAM,† M.B., CH.B.

British Medical Journal, 1970, **3**, 612-615

Summary: Hyperbaric oxygen and the vasodilating effect of tolazoline hydrochloride were used to investigate atherosclerotic ischaemia of the skin of the foot. Ischaemic feet were divided into two subgroups each with a foot blood flow significantly higher than normal and significantly different from each other. The high blood flow in the ischaemic feet appears to have been an attempt to meet a tissue oxygen need. In some instances this need seems to have been satisfied but without obvious benefit to the ischaemic or anoxic skin. It is suggested that a local rather than a regional blood flow insufficiency is the cause of skin lesions in peripheral vascular disease.

* Surgical Research Fellow.
† Senior Lecturer in Surgery.
Hyperbaric Unit, University Department of Surgery, Western Infirmary, Glasgow W.1.

Introduction

During the course of studies on the effect of hyperbaric oxygen in patients with atherosclerotic peripheral vascular disease it was observed that resting foot blood flow seemingly exceeded that of normal control subjects. This apparent paradox has been the subject of a detailed investigation.