cases, one case in particular some years ago. A youngster was not only normal, but superior intellectually. After a period of two years during which he developed diabetes and was very poorly regulated with numerous attacks of hypoglycemia, he was a "vegetable" intellectually. If this can happen in a child, imagine what hypoglycemia could do to a fetus whose brain is even more vulnerable. This might very well be the explanation of many of the abnormalities.

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EDITORIALS

THE LACTIC ACIDOSIS SYNDROMES

Lactic acidosis[1-12] results from an accumulation of lactic acid in excess of the usual concentration present in the basal resting state in health, viz., in excess of 1 mM/L. or 12 mg. per cent. It is to be added to the growing lists of metabolic acidoses of either endogenous origin (diabetic ketoacidosis, starvation ketosis, alpha ketoglutarate acidosis of hepatic failure, and perhaps uremic acidosis) or of exogenous origin (salicylate intoxication, formic acid excess of methyl alcohol poisoning, etc.). In each of these the excess of one or more such organic radicles is attended, in lesser or greater degree, by decreases in the plasma bicarbonate and *p*H, hyperventilation with lowering of the PCO_2, and transfers of water, H^+ and electrolytes between cells and the extracellular fluid, and readjustments in their renal excretion. The metabolic acidoses of the organic type are to be differentiated from the inorganic types, i.e., those resulting from excesses of chloride, inorganic phosphate, etc., or from a lowering of plasma sodium concentrations without an equivalent reduction in the so-called anion or proton donor column of the Gamble diagram.

Since interconversion of lactate and pyruvate occurs within the body by transfer of a hydrogen ion, it is usual to think of these two radicles in terms of a ratio, i.e. the L/P ratio. In the basal state in health and in certain physiologic and some pathophysiologic circumstances this ratio is approximately 10:1. In other experimental or pathophysiologic states the ratio may increase several or many fold largely as a consequence of a preponderant increase in lactate. The increment in lactate which produces this rise in the ratio can be described as excess lactate or XL.

Until such time as all possible origins of lactic acidosis are identifiable, it is very helpful to classify individual examples in accord with Huckabee's scheme[1,2] which takes into account the absolute and the relative changes in lactate and pyruvate and describes the circumstances under which specific examples of lactic acidosis have been encountered. Thus hyperventilation, exercise, and infusion of pyruvate, alkali or NaCl solution, are attended by proportionate increases in the concentrations of lactate and of pyruvate with maintenance of the L/P ratio at 10:1. These, therefore, all fall into Type I. On the other hand, experimental or clinical hypoxia, hemorrhage, impending or actual circulatory collapse, injection of epi- or norepinephrine and the administration of agents such as cyanide which block aerobic glycolysis are characterized by marked increases in the lactate and lesser rises in pyruvate with consequent increases in the L/P ratio, i.e., excess lactate (XL) is present. This is Type II A. In some of the clinical examples of Type II A removal of the incitant or attendant disorder, i.e., correction of hypoxia, reversal of shock, etc., resulted in recovery and clearance of the lactic acidosis. In others death has ensued. It is significant that fatalities have occurred even though the acidosis, i.e., the bicarbonate and *p*H decrease, is corrected by $NaHCO_3$, suggesting that in these instances death was not attributable to acidosis. The lactate levels were still elevated, of course, and it may be that this caused death. This seems unlikely, since even greater lactate increases under other circumstances such as exercise do not prove fatal. Also it is unlikely that maintenance of excess lactate levels results from inadequate renal clearance. It is more likely that the lactate excess is merely an indicator of a continued metabolic disturbance such as inhibition of the aerobic and acceleration of the anaerobic metabolism with the establishment of a steady state equilibrium in which lactic acid excesses are perpetuated.

Huckabee has also described lactic acidoses with excess lactate which were not accompanied by any of the hitherto recognized concomitant of Type II A. These he classified as Type II B. All nine of his patients died.

Lactic acidosis has also developed in patients with diabetes mellitus, under treatment with diet, insulin or in a few cases, phenethylbiguanide.[3,5,10] Since phenethylbiguanide in high concentrations in vitro can accelerate anaerobic glycolysis with increased pyruvate and lactate production[7,8] and since phenethylbiguanide will produce a slight rise in the L/P ratio, the contribution, if any, which phenethylbiguanide can make to the production of severe lactic acidosis should be considered. On the other hand, in most of the nondiabetic and diabetic patients including those who received phenethylbiguanide, in whom lactic acidosis with excess lactate has been described, circulatory collapse and tissue hypoxia were present and as indicated these alone can produce lactic acidosis. Renal insufficiency with azotemia and the exacerbation of lactic acidemia by alcohol ingestion may also produce lactic acidosis.[10] At present, therefore, there is no evidence that phenethylbiguanide itself produces lactic acidosis.

It is logical, however, to question whether the slight tendency to lactacidemia present during phenethylbiguanide therapy may accentuate lactic acidosis of hypoxic or other origin. There is no direct evidence on this point as yet. Phenethylbiguanide has been reported by Walker, Linton, and Thomson[11] to accentuate lactic and pyruvic acid accumulations induced by exercise, but these findings have not been duplicated in controlled studies in at least two other laboratories in which the drug was administered in the usual clinical dosages, 75 or 150 mg. per day.

The diagnosis of lactic acidosis and of the presence of excess lactate depends of course on the demonstration of increases in blood lactic acid. The diagnosis of lactic acidosis with excess lactate can only be made by measurements of plasma lactate and pyruvate. Unfortunately, at present these are not routine laboratory procedures. However, the possibility of lactic acidosis can be raised in a diabetic whenever the serum bicarbonate is substantially reduced without a substantial elevation in urine or plasma ketones and excluded if the bicarbonate is normal. However, as indicated earlier, not all metabolic acidoses are lactic acidoses[9] and, therefore, other causes such as accumulation of other proton donors and hyperchloremia, hyperphosphatemia, or hyponatremia must be excluded. Ordinary diabetic ketoacidosis is not generally accompanied by an increase in the lactic acid levels.

Therapy of lactic acidosis in the nondiabetic or diabetic at present consists of removal of circulatory or other impediment to tissue oxygenation, withdrawal of

all except indispensible medications, and correction of the acidosis by the administration of $NaHCO_3$. It is reasonable to consider use of the artificial kidney or of peritoneal lavage if the lactate excesses persist, though it is not established that these can alter the outcome. The injection of methylene blue to convert lactate to pyruvate with subsequent removal of pyruvate by usual metabolic routes is experimental. Dosages of 1 to 5 mg. per kilogram have been used for this purpose. Also in the diabetic the basic principles of sound management emphasized in the editorial by Marble in this Journal[12] and the caution advised in the brochures provided by manufacturers of all oral hypoglycemic agents should be observed: Seriously ill patients and those with ketosis, other than the starvation type which responds promptly to carbohydrate, should be treated with insulin.

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UNETHICAL DRUGS OR DEVICES

With the approval of the Council of the American Diabetes Association, the Committee on the Use of Therapeutic Agents invites readers of this Journal to report instances of the use of unethical drugs or devices for the treatment of diabetes which come to their notice.

Such information should be addressed as follows: Committee on the Use of Therapeutic Agents, American Diabetes Association, 1 East 45th Street, New York 17, N. Y.

BOOK REVIEW

GLUCAGON: CHEMISTRY AND FUNCTION IN HEALTH AND DISEASE. *By Piero P. Foa and Giorgio Galansino, Wayne State University Medical College and The Chicago Medical School. $6.75. Charles C Thomas, Springfield, Illinois, 1962.*

The authors of this monograph (one in the series of American Lectures in Living Chemistry, edited by Dr. I. Newton Kugelmass) have performed a service for all those interested in glucagon. They have written an extensive review of the literature regarding this substance and have compiled a bibliography (comprising 724 papers) which is of great value. The book covers all the diverse aspects of glucagon—chemistry, assay, production, secretion, destruction, effect on metabolism of carbohydrates, protein and lipid, and clinical uses.

The major emphasis concerning the mode of action of glucagon has been placed on its effect on carbohydrate metabolism with comparatively little discussion of, or speculation about, its possible role in protein and lipid metabolism. This is probably inevitable since the major portion of the research on glucagon has concentrated on its effects on blood glucose and liver glycogen. However, as the authors point out, much more research needs to be done to elucidate the effects of glucagon on both protein and lipid metabolism. The authors have made no attempt to form any unified concept of the action of glucagon on such a diverse group of physiological parameters as urinary excretion, gastric mobility, cardiac rate and contraction force, and metabolism of carbohydrates, protein and lipid. However, the factual information is presented and this monograph will certainly be of great value to those who wish to attempt such a unified theory.

Unfortunately the editor and publisher have been somewhat lax in proofreading and a number of typographical errors exist in the volume. These do not decrease the value of the work but are an annoyance to the reader.

This is not a book to be read rapidly and casually—too much information is packed into each page for that. It is, however, an excellent reference work for anyone interested in a survey of most of the research that has been published (up to 1962) about glucagon.