BIOCHEMICAL DISORDERS IN HUMAN DISEASE

Edited by

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PREFACE

Our knowledge of the processes underlying disease now takes us in many instances beyond the limits of classical cellular pathology into the realms of abnormalities resulting from disorder of the enzyme-catalysed reactions occurring within the cells. That is to say, for many diseases pathology is now passing from the stage of morbid histology to that of morbid biochemistry. This is indeed no new development, but whereas until recently only a few diseases were interpretable in terms of disordered biochemistry, the rapid strides that biochemical techniques and theory have made in recent years have greatly extended this approach to pathology. There is now a wide range of diseases in which abnormalities of enzyme action, congenital or acquired, or deviations from normal of the electrolyte balance of the body cells and extracellular fluids, have been demonstrated.

The interdependence of the fields of biochemistry and medicine is therefore becoming increasingly apparent. The biochemical approaches being made to the study of different diseases are, however, extremely varied, and the descriptions of the relevant discoveries are widely scattered through the medical and scientific literature. It seemed, therefore, that a book compiled by several authors actively engaged in the study of different disease groups was desirable. Its purpose would be to assemble, relate, and interpret the known facts concerning the biochemical disorders that underlie or are associated with human disease. At the same time, it was felt that such a book might profitably put before biochemists a number of problems that could be relevant to the course of their research, and would help them to understand the needs of present-day physicians. Apart from their importance for a fuller understanding of pathogenesis, many of the findings discussed in this book are also, of course, of practical importance in the diagnosis of disease and in the management of both medical and surgical patients. As this book was intended primarily to give medical readers a picture of how biochemistry is now impinging on medicine and surgery, it was decided to deal with the subject on an 'organ basis' rather than to take the more obvious biochemical approach of dividing the subject into disorders of carbohydrate metabolism, fat metabolism, protein metabolism, and so on. The authors of the various chapters have been asked to describe, in so far as it is possible in the light of our present knowledge, how the various diseases of any given organ-system are dependent on biochemical disorders and to indicate the trends of biochemical work now in progress in these contexts. The approach varies somewhat from chapter to chapter since each author has been free to deal with his own particular subject in the way best suited to it.

It is obvious, of course, that certain diseases lend themselves more readily than others to biochemical analysis, so that the facts that have

been garnered will vary in volume and in significance in different diseases. The treatment of some diseases in this book may therefore appear to be more complete than that of others. But we would ask our readers to remember that we have been limited not only by the varying degrees to which chemical pathological work has progressed in different fields but also by having to keep the book within a reasonable size. No separate chapters for example have been allotted to diseases of the skin, to infectious diseases, to gerontology, or to cancer, although certain aspects of these topics are dealt with in connexion with the diseases of different organs. Neither, in general, are detailed descriptions included of biochemical methods used in clinical pathology, although the clinical aspects of the more important biochemical investigations are given in outline or by reference and the relevant analytical findings discussed.

As editors we would like to take this opportunity of thanking the authors, who have collaborated with us in producing this book, for their ready co-operation and their forbearance; and as British editors we would like in particular to thank our American authors who have so willingly permitted their manuscripts to be 'anglicized' as regards certain spellings and usages.

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We also wish gratefully to acknowledge the help we have received from our secretaries, Miss Rosemary Tilden and Mrs. Beryl Blake, our assistants, Miss Patricia Kind and Mrs. Margaret Sutton, and finally to thank our publishers, Messrs. J. & A. Churchill Ltd., of London, and The Academic Press, Inc., of New York, for their good-natured assistance and valuable advice throughout the preparation of this book.

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CONTENTS

CHAPTER I

DISEASES OF THE GASTRO-INTESTINAL TRACT

by

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BEFORE committing ourselves to an end-to-end survey of the alimentary tract, we may perhaps take note of one or two general features which go a long way towards accounting for the importance of this system in normal and disordered metabolism. The alimentary tract can be most simply looked on as a convoluted tube whose walls are indeed part of our body, but whose lumen is functionally outside the body; to say this is not to state an anatomical paradox, but to emphasize that the alimentary lumen provides a situation in which reactions can proceed under chemical conditions, notably of hydrion concentration, which would not be tolerable within the body proper. In fact, the main function of the system is to convert a great variety of foodstuffs, digestible but not assimilable, into substances which can be absorbed into the blood or lymph without provoking chemical or immunological reactions. The appearance of food stimulates the secretion of glands lining or communicating with the alimentary lumen; digestible foods are broken down to absorbable substances; and these are then absorbed, in some cases by active processes against concentration gradients. The orderly sequence of these processes is quite essential to life, for we can only maintain our organization and activity by spending the energy stored up by other animals or by plants in their own tissues; disease of the alimentary tract can therefore lead to starvation, if all foods are affected, or to malnutrition if specific food factors fail to be assimilated.

Our necessary supply of water and mineral salts is also taken in by the alimentary tract, and deprivation of these is just as serious as starvation, though its effects are quite different. Simple deprivation of water and electrolytes is commonly aggravated by loss of alimentary secretions by vomiting or diarrhoea, or through fistulae or drainage tubes. These secre-

tions contain not only enzymes but also mineral salts in proportions apt to provide a suitable milieu for the digestive process; so that their loss causes both electrolyte depletion and acid-base disturbance. In fact, gastro-intestinal disease is responsible for the commonest and the most serious disturbances of water and electrolyte metabolism. This is scarcely surprising when we consider the frequency of disease of this system, and also the amount of secretion potentially involved. Classical estimates of the total daily alimentary secretions reach 8200 ml. (Gamble, 1947); and the large amounts of fluid which can be withdrawn by suction drainage show that this amount is at least within the secretory ability of the alimentary tract.

Interference with absorption and loss of secretions may be regarded as pathogenic processes specific to the alimentary tract; disease there can also affect metabolism in ways common to other tissues. A substantial proportion of all neoplasms originate in the alimentary tract, and infective lesions are also common; and the many operations done on the alimentary tract evoke their characteristic metabolic response (Moore & Ball, 1952). But perhaps we have said enough to suggest the general importance of this system in clinical chemistry, and to justify a more detailed approach to specific problems. The arrangement of our survey will be broadly regional, dealing with the main anatomical subdivisions of the alimentary tract in series; but for economy of presentation we will give only one description of syndromes such as potassium (K) depletion, although this can arise in association with diseases of quite different parts of the alimentary tract.

MOUTH, SALIVARY GLANDS, PHARYNX AND OESOPHAGUS

These portions of the alimentary tract are occupied in converting food, which may be quite lumpy as eaten, into a form which is physically rather finely divided, so that the digestive juices can come into real contact with it. Apart from foods which really demand a lot of chewing, the transit time of foods in this part of the alimentary tract is so short that very little true digestion can take place. The physical effort of mastication is supplemented by salivary secretion, which moistens dry foods, and also lubricates their passage with mucin. Although the salivary secretion contains amylase, this can have little time to act before the food reaches the stomach; there is evidence, however, that digestion by salivary amylase may proceed for some minutes in the stomach before gastric hydrochloric acid (HCl) has penetrated the bolus sufficiently to inhibit ptyalin activity; and 60–70% of ingested starch may be converted to maltose in this way. Certainly the main interest until the food has entered the stomach lies in the physical transformation of foods into a digestible form; the dyspeptic effects of hurried meals, lack of teeth, and inefficient dentures are well recognized. We need discuss here, however, only the secretion of saliva, the chemical basis of hunger and thirst, and the metabolic effects of oesophageal obstruction.

Salivary secretion

Few subjects in physiology can have been studied so intensively, and made the basis of such seminal generalization, as the stimulus to salivary secretion in Pavlov's dogs (Babkin, 1951). We can notice this only in passing, however, for conditioned reflexes have not so far declared themselves

as a chemical problem; yet it seems clear that the composition and amount of saliva formed is dependent on the nature and quantity of the stimulus exciting secretion. With a local stimulus like salt or hydrochloric acid applied to the buccal mucosa, the amount and chloride concentration of the saliva increase with the concentration of the stimulant solution. Meat extract in dogs is a more effective stimulant of salivary secretion than is milk. The salivary secretion is modified both by sympathetic and by parasympathetic stimulation (Babkin, 1950); there is no evidence of hormonal stimulation of the salivary glands, and the immediacy of the salivary response makes such a stimulus unlikely. The amount of saliva is usually given as 1–1·5 l./day. The electrolyte composition of saliva is variable, but on average it contains about 5 times as much K as does plasma, and $\frac{1}{10}$ as much Na; it represents a true secretion, as opposed to an ultrafiltrate. In contrast to chloride, iodide is considerably concentrated in the saliva, compared with the plasma, and this concentration of iodide can be depressed by drugs which inhibit uptake of iodine by the thyroid (Rowlands, Edwards & Honour, 1953). Perhaps the most important organic constituent of saliva is mucin, but a salivary amylase is present in man, though not in dogs or cats. The formation and composition of saliva have been reviewed by Jenkins (1954).

Hunger and thirst

Most of us in health get some enjoyment out of a good meal; and, as McCance (1953) has indicated, the problem for many of us is how to stop eating, rather than to know why we started. The sensations of hunger and satiety must have a chemical basis, probably not a simple one, such as the blood-sugar level, but perhaps, as McCance has suggested, a replenishing of nerve-cells with oxidizable, osmotic, or structural materials. Hypothalamic centres controlling appetite have indeed been demonstrated, but we have still to discover the chemical stimuli which bring them into action, and the chemical or other mechanisms through which they affect behaviour. Thirst offers at first glance a simpler problem, in that we are clearly dealing with the deficit of a single substance, and not of an unidentified component of a complex metabolic mixture; but it is not yet entirely proven that thirst is something more than a local dryness of the mouth and throat, as was proposed by Cannon (1918). It has been shown, indeed, that thirst is not relieved by sham-drinking, in which water given by mouth is allowed to escape through an oesophageal fistula (Towbin, 1949). Moreover, thirst is produced by the injection of hypertonic solutions, not only of salt (Wolf, 1950) but also of sorbitol and sodium sulphate or acetate (Holmes & Gregersen, 1950). These findings suggest that thirst is caused neither by local dryness of the mouth nor by an absolute deficit of water in the body; but rather by a shrinkage in the water content of the cells, such as is induced by hypertonic expansion of the extracellular fluid. It is likely that the absolute amount of water in the cells is less important than the osmolarity of cell fluid; for thirst is not experienced in experimental K depletion, in which the water content of the cells is indeed lowered, but not to so great an extent as the base content (Black & Milne, 1952). At present, increased osmolarity of cell fluid seems to be the stimulus to the sensation of thirst; but we do not know the mechanism of response to this stimulus, nor whether it acts on tissue cells generally, or,

as seems more likely, on special groups of cells analogous to the osmo-receptors which control pituitary antidiuretic activity (Verney, 1947).

Oesophageal obstruction

Even intermittent and partial obstruction, as in cardiospasm, leads in time to severe malnutrition; and progressive or total stricture, as in cancer or corrosive poisoning, causes rapid wasting, with thirst and constipation. The advancing cachexia no doubt stems mainly from direct failure to ingest food and fluid effectively; but it is aggravated by loss of saliva in the regurgitated food, by increased protein breakdown in a necrotic and infected tumour, and sometimes by haemorrhage. The effects of general lack of calories usually predominate over any specific deficiency of proteins or vitamins. Beyond mentioning its occurrence, we need not discuss malnutrition here, as it is the subject of a later chapter in this volume, and has also been reviewed at some length by McCance's group (M.R.C., 1951), and at length by Keys, Brozek, Henschel, Mickelsen & Taylor (1950).

STOMACH

The stomach is essentially an organ of digestion, and not of absorption. The fundus of the stomach can be considerably distended with food, without provoking vigorous contractions, whereas the pyloric antrum is capable of breaking up masses of food which have escaped mastication. The end result of gastric digestion is a material which is mechanically and chemically acceptable to the small bowel, where digestion is completed and absorption begun. Small amounts of chyme probably pass the pyloric sphincter soon after food has entered the stomach; but it is not until gastric digestion has resulted in general liquefaction of the stomach contents that massive gastric emptying takes place. Gastric digestion is carried on in an acid milieu, but, as the time for gastric emptying approaches, the stomach contents are considerably neutralized by the alkaline secretion of Brunner's glands, regurgitated from the duodenum. We cannot consider here the motor functions of the stomach, nor its relation to haemopoiesis; but we must notice those features of gastric secretion which are important in the pathogenesis or in the disordered biochemistry of stomach disease.

Physiology of gastric secretion

The surface epithelium of the stomach, and the glands in the cardiac and pyloric mucosa, produce an alkaline mucinous secretion (Hollander, 1950). The glands in the fundus contain 'parietal' or 'oxyntic' cells, which produce a secretion containing 160 m-equiv./l. of hydrogen ion, 170 m-equiv./l. of chloride, and 10 m-equiv./l. of potassium (Fisher & Hunt, 1950); and also the 'body chief cells', which contain zymogen granules, and secrete pepsin. The gastric juice is a mixture of these various components, in proportions which vary with the degree of nervous and hormonal stimulation; even these variations in gastric secretion do not exhaust the variability in stomach contents, which contain not only gastric secretion, but also swallowed food and saliva, and regurgitated material from the duodenum. These considerations make it difficult at times to interpret the results of test meals or of analysis of fasting juice; they have also constituted a problem in the investigation of the separate contribution made

by different regions of the stomach, and different cell-types. By observing the composition of gastric juice under different conditions, Gray & Bucher (1941) calculated that 'parietal' cell secretion was an almost pure 0·16 N solution of hydrochloric acid; while 'non-parietal' secretions have an electrolyte composition similar to that of a plasma ultrafiltrate. Both secretions are virtually isosmotic with plasma, and variations in gastric acidity during fasting are determined by the proportion of parietal to non-parietal secretion, rather than by change in the composition of the separate secretions.

The digestive activity of the stomach depends partly on the enzyme content of the gastric juices, and partly on the formation of free HCl. These combine to effect a partial hydrolysis of protein to the polypeptide stage. The characteristic enzyme of gastric secretion is pepsin, formed from the zymogen granules of the 'body chief cells' as an inactive precursor pepsinogen, which is converted to active pepsin in an acid medium. Pepsin has optimum activity around *p*H 2, and so is active at the acidity observed in stomach contents at the height of gastric acid secretion. Although gastric digestion mainly involves proteins, the early stages of starch hydrolysis may be continued by salivary amylase until this action is cut short by increasing acidity. Although gastric lipase has been described, its *p*H optimum is said to be high, and it is doubtful if any effective fat splitting occurs in the stomach in adults, though in the less acid stomach of infants some lipolytic activity may be present. The same considerations apply to gastric rennin, with its *p*H optimum at 6–6·5. Also, the rennin content of adult gastric juice in man is negligible, and it is doubtful if the practice of citrating milk to prevent rennin activity by removing ionized Ca is of any practical value.

The process of HCl formation by the oxyntic cells has been reviewed by Davies (1951, 1952), and also by Hollander (1952), Conway (1953) and Heinz & Öbrink (1954). As Davies (1952) points out, there have been nearly 40 hypotheses put forward to account for HCl secretion, many of which have had to be discarded as insufficient to account quantitatively for a process which is capable of forming rapidly a secretion in which hydrogen ions (H^+) are more than 4 million times as concentrated as they are in blood. It has been shown that although the oxidation of glucose could account for some H^+ formation, and breakdown of organic acids makes some contribution, the possible H^+ formation from such sources does not approach the observed rate of H^+ secretion, and in fact the only substance available to yield H^+ in adequate quantity is water. An equivalent amount of hydroxyl ion (OH^-) would be formed at the same time, and normally this is neutralized by carbonic acid derived from CO_2. It is in the neutralization of concurrently formed OH^- that carbonic anhydrase may become a limiting factor; when carbonic anhydrase is inhibited, H^+ formation proceeds normally for a time, but is later arrested by damage to the cells by alkali which can no longer be effectively removed. The formation of bicarbonate anion in amounts equivalent to the H^+ found was demonstrated in tubes of frog gastric mucosa, and is reflected qualitatively in the well-known 'alkaline tide' in blood and urine which accompanies gastric activity. According to Davies (1952) the process of separating H^+ and OH^- 'requires (1) a means of transporting H atoms (electrons + protons) across the pericanalicular zone of the oxyntic cells, (2) a means of

returning the electrons to the starting-point near the cell wall, and (3) a source of power sufficient to drive the processes for acid formation'. Hydrogen transport could be carried out by the reversible conversion of oxaloacetate to malate, or some similar system. Electron transport could be achieved by the reversible conversion of ferric to ferrous iron in the cytochrome system, and the change in valency here would make available chloride ion (Cl^-) for secretion with the H^+. The energy requirement could be met from high-energy phosphate bonds. It will be apparent that these arrangements are very generally available, but in the oxyntic cell they must be spatially orientated so that H^+ ions present themselves for excretion into the canaliculi, while OH^- ions are converted to bicarbonate in a part of the cell where the resulting bicarbonate can readily be removed into the blood-stream, in exchange for Cl^-.

Given the secretion of H^+ and Cl^-, transfer of water would follow osmotically (Davies, 1952). The osmotic aspects of gastric secretion have been considered more fully by Rehm, Schlesinger & Dennis (1958), who found that application of hyper- and hypotonic salt solutions to the resting mucosa resulted in very small rates of water transport compared with those observed during actual secretion. This finding is inconsistent with a view previously advanced by Rehm (1950), that parietal cells secrete H^+, and Cl^- is contributed by the surface epithelial cells; in place of this Rehm and his colleagues now suggest that parietal cells secrete Cl^- and surface epithelial cells H^+. This view seems unlikely in that surface epithelium is not limited to the acid-producing fundus; and it also conflicts with the observations of Teorell & Wersäll (1945) that acid formation persists after stripping of the surface epithelium, and of Bradford & Davies (1950) that the canaliculi of the parietal cells contain a strongly acid fluid during secretion.

Gastric secretory activity may be initiated and maintained both by nervous impulses and by hormone action. In the 'cephalic phase' of gastric secretion, the stimulus is nervous, mediated by the vagus, and this type of gastric activity is abolished by a successful vagotomy. Nervous secretion can be stimulated by the sight, smell, or thought of food, by taste and swallowing of food, and also by stimulant drugs such as caffeine. The absence of a response to caffeine, and to insulin-induced hypoglycaemia, indicates that vagus innervation of the stomach has been adequately interrupted (Stein & Meyer, 1948). Regeneration of vagal nerve supply to the stomach is very common after vagotomy, and this procedure has been practically abandoned as the sole operative treatment of peptic ulcer, since it may also cause gross interference with gastric emptying; vagotomy may still be carried out to supplement gastrectomy or gastro-enterostomy. Apart from operation, vagal stimulation of the stomach can be prevented by atropine, but at a dosage which causes dryness of the mouth and mydriasis. The effect of emotion on gastric acidity may include not only vagal stimulation but also inhibition by sympathetic fibres (Cannon, 1909). The net effect varies greatly in different subjects (Wittkower, 1931), and even in the same subject the gastric response may vary at different times and with different stimuli (Wolf & Wolff, 1943). Emotional stress may affect gastric secretion by a hormonal as well as by a neurally transmitted stimulus, for adrenal steroids increase the volume and acidity of gastric secretion (Gray, Benson, Spiro & Reifenstein, 1951).

In addition to nervous stimulation, gastric acid secretion can be stimulated by distention of the stomach, by foods such as meat, which contains 'secretagogues', and by hormones arising in the stomach and in the small intestine during digestion. Hormonal control of gastric secretion has been reviewed by Gregory (1952). The mucosa of the pyloric antrum is probably the source of much of the 'gastrin' formed (Gregory & Ivy, 1941); and this is of some practical importance, as the recurrence rate of ulceration after partial gastrectomy is much higher with operations in which the pyloric mucosa has not been ablated. Ivy, Grossman & Bachrach (1950) have collected figures showing a recurrence-rate of 39% after operations in which the pyloric mucosa was retained, in contrast to only one recurrence in 79 patients who had the pyloric mucosa excised. It is not clear whether the hormone evolved in the pyloric mucosa, and known as 'gastrin', is in fact entirely histamine, or whether other hormonal stimulants, as yet unidentified, are also concerned. There exists also a hormonal mechanism for gastric inhibition, in which the stimulus is the presence of fat in the upper small intestine, and the hormonal mediator is known as 'enterogastrone'. The chemical nature of this hormone is not known, and it has not been isolated; as Gregory (1952) points out, there is no definite evidence that the various extracts of intestinal mucosa which inhibit gastric acidity do in fact contain the physiological hormone. Inhibiting substances (urogastrone and anthelone) have also been demonstrated in urine, but their relation to physiological gastric inhibition is less certain than that of duodenal extracts. Therapeutic applications of these natural gastric inhibitors have given unconvincing results, and success along this line probably awaits more satisfactory characterization of the substances involved.

Assessment of gastric secretion in man

Experimental work on gastric secretion has been largely based on the secretion in isolated gastric pouches, where contamination by saliva, food and regurgitated intestinal fluid can be rigorously excluded. Contamination of this type undoubtedly influences the findings in 'fractional gastric analysis' as routinely performed, so that conclusions drawn from such procedures must be cautiously interpreted. The position is further complicated by variable rates of gastric emptying, and by the composite nature of gastric secretion. For instance, an increase in the *concentration* of acid in gastric samples tends to occur at a time when the actual *rate* of HCl secretion is falling off steeply, but the volume of stomach contents is shrinking still more rapidly as a result of diminished volume of secretion and gastric emptying. Even absence of free HCl in gastric samples may be produced as an artefact, when sufficient non-parietal secretion is produced to neutralize the hydrochloric acid formed (Hunt, 1952). This last contingency is probably somewhat uncommon, for 3·5 parts of non-parietal secretion are needed to neutralize one part of parietal secretion. It may, however, account for the finding of James & Pickering (1949) that in patients with gastric ulcer the stomach contents are often neutral at night, in contrast to normals and patients with duodenal ulcer; there is evidence that gastric ulcer patients secrete more of the alkaline non-parietal secretion than do normal subjects in response to histamine and insulin (Hunt, 1950). Our understanding of gastric secretion in man has been enlarged by procedures which are too complicated to form a part of routine clinical