acting type, the presence of which characterizes the obstructive and hepatogenous forms of jaundice. Rich has designated as "retention jaundice" those types in which there are indirect van den Bergh reactions and acholuria and has characterized those types in which there are direct-reacting bilirubin and bile in the urine as "regurgitation" jaundice. The inference of this classification is obvious.

Exactly what chemical differences exist between these two types of bilirubin is still unknown; one theory holds that bile acids, which are presumably present in excess in the blood of patients who have obstructive or hepatogenous jaundice, lower the surface tension of the bilirubin molecule and thus change its chemical behavior. Another theory is based on the assumption that indirect-reacting bilirubin is in combination with protein which retards the direct van den Bergh reaction and inhibits renal filtration. Supporters of this view hold that passage of indirect-reacting bilirubin through the hepatic cells removes this combined protein and leaves the "regurgitated" bilirubin in a form free to pass the kidney and alter in color when Ehrlich's diazo reagent is added to the serum. The recent studies of Duesberg lend support to the latter hypothesis; his observations indicate that in the degradation of hemoglobin iron is first split off while the globin fraction remains in combination as far as the formation of bilirubin.

Is all of the bilirubin present in the blood of patients with obstructive or hepatogenous jaundice in the direct-reacting form? That is, has it all passed through the cells of the liver and been regurgitated into the blood stream? If current conceptions of dysfunction of the cells of the liver in the presence of obstruction or toxic injury are correct, this should not be the case, but part of the bilirubin in the circulation should be the indirect-reacting form which is produced by physiologic wastage of corpuscles and dammed back into the circulation because of the physiologic or pathologic inability of the hepatic cells to take it up. The photometric studies recently reported by Osterberg appear to indicate that a part of the circulating bilirubin in cases in which jaundice is due to mechanical obstruction and parenchymatous lesions of the liver gives an indirect reaction, while another fraction apparently has passed through the liver cell, as shown by a direct van den Bergh reaction. While further chemical and spectrophotometric studies of differences existing between directly and indirectly reacting bilirubin will doubtless be required to establish the authenticity of these methods, it does seem clear that the quantitative determination of the two forms of bilirubin in a single specimen of serum is not beyond the bounds of possibility. Such information when it becomes available will probably be of considerable clinical importance. It may be that the amount of one or the other types of bilirubin present in the individual case is of prognostic significance and may give information which the total figures, now in use, do not supply. These and similar studies naturally will lead to some revision of present views regarding the mechanics of "regurgitation" jaundice; they emphasize the importance of learning what disposition is made of the porphyrin and iron-containing complement of the hemoglobin molecule, and, finally, they indicate that the complexity of the problem of bilirubinemia increases as more is learned of its essential chemical nature.

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REFERENCES

THE ETIOLOGY OF PEPTIC ULCER

A NEW statement on the etiology of ulcer is possible in the light of recent developments in gastric physiology. Mann's experimental production of ulcer, now widely confirmed, showed the paramount importance of the acid factor in the immediate causation of ulcer in dogs. There is good evidence of a similar mechanism in man. Experience with really continuous, night and day, neutralization of gastric acidity as by the aluminum hydroxide drip in the clinical treatment of uncomplicated ulcer indicates that Mann's experimental results may be fairly satisfactorily duplicated. That is to say, healing occurs quite regularly within one to two weeks. This would seem to establish the fact that the erosive action of acid gastric chyme is the sine qua non of actual ulceration and the whole immediate cause of clinical ulcer and that all other factors act as predisposing causes. From the practical standpoint the predisposing causes may be of great importance, quite overshadowing the immediate and specific cause, since, when they are removed, the ulcer may heal spontaneously or on account of the restoration of the normal neutralizing mechanism of duodenal regurgitation. Moreover, proved cases of peptic ulcer in proved cases of constant anacidity probably do not exist. Reports of such cases even on single examinations are so rare as to negative their significance.

Etiological factors in ulcer have usually been referred to as neurogenic, vascular, infective, toxic, glandular, traumatic and others including a mysterious X factor. The old physiological query of "why doesn't the stomach digest itself?" is probably best answered by the statement that it does when its defenses are down. The above predisposing factors lower local resistance or disturb the normal neutralizing mechanism so that acid peptic digestion occurs. A localized arterial occlusion might lead to ulcer in the stomach wall while the same process in less exposed tissues might cause no lesion or an innocent infarction. Likewise, an organic lesion in the sub-thalamic area of the brain or purely functional psychic impulses may induce vasomotor or trophic changes in the gastric mucosa with a profound lowering of local resistance. Nervous factors, which every mature clinician knows are most important in ulcer may operate in part by inducing pylorospasm and retarding acid secretions for abnormally long periods.

Such overshadowing of a specific cause by conspicuous predisposing causes is not rare in medical science. For example, "traumatic arthritis" as described by
Hilton in his “Rest and Pain,” before the discovery of the tubercle bacillus quite adequately explained joint tuberculosis as the result of injury. The teaching survives to this day in the beliefs of most victims of Pott’s Disease. How reluctantly even the medical profession of that day yielded to the bacterial “theory” of disease.

It is extraordinary that Sippy with his conviction upon the importance of the acid factor in ulcer did not devise a method of really continuous night and day neutralization. Ulcers apparently heal at a rate that is proportional to the constancy of neutralization. Some ulcers heal spontaneously, others heal by part-time neutralization as by the Sippy routine, but the largest percentage of cures in chronic cases and in the shortest period of time is obtained by really continuous neutralization. This removes the immediate cause of ulcer and permits prompt healing. The predisposing factors should then be attended to as far as possible. This is a reversal of the process or of the sequence of events leading up to and causing ulcer. Secondary complications such as extensive cicatrization or obstruction really present a separate problem, usually surgical and play no role in the primary pathogenesis of peptic ulcer.

Meuhlenbracht’s remarkable reduction of mortality from hemorrhage by feeding the bleeding ulcer case liberally and by the use of alkalis is probably due to an approximately continuous neutralization and arrest of gastric motility.

Really continuous night and day aluminum hydroxide drip has been most effective in controlling persistent and recurrent bleeding. There is apparently a prompt cessation of the erosive process and of digestion of the newly formed clot in the bleeding vessel.

This conception of the etiology of ulcer has practical implications since there has been, even among gastroenterologists, a half-hearted conviction as to the importance of the acid factor and a half-time use of antacids with half-way results. Thorough use of continuous neutralization for prompt healing of the open lesion permits of a more rational follow-up leading to individualized treatment of the whole patient. Attention to the predisposing causes of disturbed gastric physiology is then of the first importance in the prevention of recurrences.

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SOME COMMENTS OF OSLER ON CIRRHOSIS

Medical history has preserved for us the opinions of a small group of men who have had an instinctive knowledge of disease processes far in advance of the thought and teachings of their time. Of these men Sir William Osler stands closest to the recent generation; there are few investigators who are not in his debt, and who have not found in his writings an expression of some concept believed to be new. Some of his opinions on cirrhosis of the liver, written in editorial form in the Philadelphia Medical News a half-century ago, are in such accord with modern thought and practice that it seems worth while to call attention to them again after this long lapse of time.

Of ascites, which is still the symptom which first attracts attention to the disease, he has this to say, “The factor which determines the onset of dropsy in cirrhosis of the liver is not always clear. The highest possible grade of portal obstruction, even obliteration of the vena portae may exist without it.... We must look beyond the liver for the explanation of these facts.... The dropsy may be due to a transitory and remediable cause.” It is still difficult to give a full and satisfactory explanation of the ascites due to hepatic damage, but it is increasingly clear that the answer is to be sought in a study of the factors which control the passage of fluids across living membranes. Hypoprothrombinemia and reduced osmotic pressure have recently been shown to be of great importance, and it now seems that there is a rough inverse relation between the latter factor and the rate of transudation. Inert substances, such as acacia, will raise the colloid osmotic pressure of serum and thereby tend to retain fluid within the capillaries; its use in the ascitic stage of cirrhosis is as yet in the experimental stage, but if nothing else is accomplished, studies on this point will afford a means of investigating the significant factors in the pathologic physiology of the formation of transudates.

The membranes involved have still to be studied; it is conceivable, but not altogether likely, that the solution to the problem will be found there. This possibility did not escape Osler’s attention; he considered the possibility that, “owing to changes in the serous layer the capillaries are rendered more permeable and without any increase in the blood pressure permit of transudation.” That anoxemia, now known to be a fairly constant finding in cirrhosis, may be partially responsible is suggested by the studies of Landis who showed that reduction in the oxygen content of the tissues greatly increased the rate of filtration through frog’s mesentery.

Commenting on the prognosis in cirrhosis, Osler was convinced that “the disease may be arrested or even cured” and noted “the personal equation.... of the liver tissue” in respect to hepatotoxins. The observations of Bollman on animals with experimental cirrhosis have fully confirmed the possibilities of arrest or cure; he has demonstrated that the pathologic process in the liver can be carried to an almost fatal conclusion; the animals being thereafter restored to normal health and their livers regenerated to a very considerable degree by the use of high carbohydrate diets and glucose given intravenously. Similar clinical results are on record, as Chester Jones has recently shown. Osler feared that, “We probably have not any remedies at our command capable of curing a cirrhotic liver,” a point with which all must agree, but it does seem possible to control the symptoms of the disease and induce some degree of repair of the liver itself in certain cases. So far as the variations in the resistance of some animals and individuals to hepatotoxic substances is concerned, this may depend upon dietary habits and the glycogen content of liver tissue; it has been clearly shown that experimental fatty degeneration of the liver requires for its production a diet low in carbohydrate and protein and high in fat and that a high carbohydrate diet will protect the organ against the most severe insults.

Osler’s remarks on treatment emphasize some particularly important points; he disapproved of the practice of deferring paracentesis “until diuretics and