acting type, the presence of which characterizes the obstrusive 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 with histamine 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 retaining 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 pro-
fession 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
devisé 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 con-
tinuous neutralization. This removes the immediate
cause of ulcer and permits prompt healing. The pre-
disposing 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 cicatriz-
ation or obstruction really present a separate problem,
_usually surgical_ and play no role in the primary patho-
genesis of peptic ulcer.

Meuhlengracht’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 hydrox-
ide drip has been most effective in controlling per-
sistent and recurrent bleeding. There is apparently a
prompt cessation of the erosive process and of diges-
tion 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 gastro-
enterologists, a half-hearted conviction as to the im-
portance of the acid factor and a half time use of
antacids with half way results. Thorough use of con-
tinuous neutralization for prompt healing of the open
lesion permits of a more rational follow-up leading to
individualized treatment of the whole patient. Atten-
tion to the predisposing causes of disturbed gastric
physiology is then of the first importance in the pre-
vention 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 instinc-
tive knowledge of disease processes far in ad-
vance 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.

Hypoproteinemia 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 con-
considered the possibility that, “owing to changes in the
serous layer the capillaries are rendered more per-
movable and without any increase in the blood pres-
sure 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 path-
ologic process in the liver can be carried to an almost
fatal conclusion; the animals being thereafter re-
stored 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 par-
ticularly important points; he disapproved of the
practice of deferring paracentesis “until diuretics and