Hepatic function is impaired so little that there is good comparison with ether and the barbiturates. Even when a liver has been purposely damaged by chloroform, avertin causes very little additional impediment.

More may be said about the liver in its activity. During anaesthesia phosphoric acid appears to leave the muscles and to sojourn in that gland until the resumption of kidney function after the recovery of an animal, when it is redistributed and partly excreted,¹⁶ and Mann¹⁷ has given it out that ether produces demonstrable effects on hepatic activity; it causes a hyperglycaemia dependent wholly on the liver, and it also depresses hepatic function in regard to the secretion of bile.

These informative data could easily be amplified: however, they may be sufficient for the present, and this fact remains, that we should not decry any one drug too much. I am convinced that even chloroform has a definite place in anaesthesia.

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A NOTE ON HEPATIC INSUFFICIENCY WITH SPECIAL REFERENCE TO EFFECTS OF DRUGS USED IN TREATMENT OF ARTHRITIS, GOUT, AND RHEUMATISM

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The urgent attention of the medical profession and of the manufacturers of reputable drugs should be drawn to the series of papers relating to jaundice, cirrhosis, and even acute yellow atrophy of the liver after the assimilation of various drugs of the cinchophen group administered in the treatment of arthritis, gout, and rheumatism. The widespread use of derivatives of cinchophen both in the frank legitimate form and in numerous patent remedies has become a serious danger. Already Weis¹ has recorded ninety-two cases of such poisoning, of which forty terminated fatally.

One is tempted to say that our knowledge of the metabolic processes in an organ is inversely proportional to its size. We now have much accurate scientific information concerning the exact function of the constituent parts of so small a gland as the pituitary, both as regards the pars anterior and the pars posterior. Anatomy, physiology, and pharmacology have kept in step during the dramatic progress of the last quarter of a century. In the case of the suprarenal gland progress has not been so

rapid, but from the days of Oliver and Sharpey on the one hand and Addison on the other we have lived to see the spectacle of the victims of Addison's disease returning from the death-bed to routine work as a result of the administration of the suprarenal extract of Pfiffner and Swingle.

In the case of so large an organ as the liver our lack of definite knowledge is astounding. Mann and Bollman² state that the known functions of the liver, named in the order in which they appear to be most easily impaired, are: (1) the ability to destroy uric acid; (2) the excretion of bile pigment; (3) the ability to prevent reaction from the administration of certain toxic substances. Mann and Bollman have rightly emphasized the dangers of talking of a functional test for the liver when the function of the liver is unknown.

Tests of hepatic function have grouped themselves around the problem of jaundice, sugar tolerance, protein metabolism, hepatic excretion of dyes, and detoxicating action of the liver on certain ingested drugs. The numerous tests depending on the excretion of bile pigment have of late been overshadowed by the van den Bergh reaction. The van den Bergh test is not purely and simply a test of hepatic function. There is more bile pigment made in the spleen and marrow than in the liver. The rate at which bilirubin is formed and the site of maximum formation are variable. The subtle differences in the pigment which determine the recurrence of a direct or indirect van den Bergh reaction are not yet fully understood. In some animals a direct reaction is obtained from the gall-bladder, and only an indirect reaction with the bile obtained from the hepatic ducts. The bile from some animals which do not possess a gall-bladder, such as the rat, never gives a direct van den Bergh reaction. The van den Bergh reaction is as inexplicably fortuitous as the Wassermann reaction—but less reliable.

The liver is concerned with the maintenance of the blood sugar at a particular level in much the same way as the kidney tubule is concerned with maintaining the salt content of the tissue fluids, the parathyroid with the calcium content, or the respiratory centre with the CO₂ content of the blood. There is no test of hepatic sufficiency in relation to carbohydrate metabolism which is reliable. Such tests involve not only the glycogen of the liver but also the glycogen of the muscles and the peculiar factors imposed upon carbohydrate metabolism by the islet tissue of the pancreas and the anterior lobe of the pituitary. Neither blood sugar level, glycogen mobilization, glucose tolerance, nor laevulose tolerance are fundamental tests for hepatic efficiency. When the function of the pancreas is impaired, as in diabetes, the liver actively maintains a higher blood sugar level, so that any further addition of glucose to the blood stream does not furnish evidence of hepatic deficiency. Conversely, after enforced starvation the rate at which injected glucose returns to pre-injection level is greatly retarded, and the degree of retardation is greater in the normal liver than in the diseased liver. The laevulose test is somewhat vitiated by the variation in the time taken by laevulose to replace glucose.

The ammonia and urea of the blood and urine, although closely associated with metabolic processes occurring in the liver in relation to protein metabolism, have failed to give reliable information concerning hepatic function as distinct from renal function. The destruction of uric acid in the normal animal seems to be entirely dependent on the presence of the liver, since no uric acid is destroyed in the absence of the liver. The complete removal of the liver of dogs produces a great increase in the uric acid content of the blood and tissues and causes the appearance of large amounts of uric acid in the urine, yet Mann says that the amount of uric acid in the urine

of persons on high purin diets *might* serve as some index of hepatic deficiency.

From the time of William Hunter of Charing Cross Hospital up to the present, a succession of dyes have been employed as tests of hepatic function. Although rather more sensitive than the simple van den Bergh, recent work with bromsulphalein and the older phenol-tetrachlorophthalein has failed to detect any but gross amounts of damage to the liver. Increase in the quantity of dye injected leads to toxic phenomena due to the dye itself. Such cases have not been unknown in the recent cholecystographic studies. It is unnecessary to discuss the extent to which cholecystography as a fairly reliable test of the function of the gall-bladder has been unwarrantedly confused with the question of function in the liver.

This apparently adverse criticism of the valuable laboratory aids to diagnosis in liver disease is designed to emphasize the importance of clinical signs and symptoms of hepatic disease. Jaundice and the general low level of metabolism; the flatulence, nausea, and slowness of pulse; the urine, the stools, the itchiness of the skin, the marked depression, the "jaundiced eye"—these are as reliable as some of the laboratory tests. It is permitted to quote that "laboratory guides are mostly artificial, are reliable in only some instances, and are the handiwork of man; clinical symptoms are the natural, infallible, unalterable expressions of definite states, and are the ways of God."

The liver occupies a unique anatomical position for registering changes due to material ingested from the alimentary canal. All the blood from the digestive tract must pass through the liver. The extensive capillary bed of the liver is interwoven with the innumerable hepatic cells so that noxious substances entering the portal venous system from the gut may undergo immediate chemical transformation into innocuous substances, or even excretion via the hepatic cell into the bile canaliculi without entering the general circulation. Quite apart from the problems of the liver circulation which have been studied in the normal by Cameron and Mayes,³ in cirrhosis by McIndoe,⁴ and in the isolated perfused liver preparation by Dale,⁵ there still remains the implication of the startling statement made by Starling that the liver may hold one-quarter of the total lymph of the body. If we accept the work dealing with the distribution of antibodies in the liver, such as that of Freund and Whitney,⁶ there is still no fundamental anatomical or physiological study of the part played by the liver in the formation of lymph.

This brief note on the function of the liver has been prompted by the rapid accumulation of cases of jaundice, cirrhosis, or atrophy of the liver as a result of the administration of drugs of the cinchophen group. Many cases of non-fatal toxicity due to their use are probably unrecognized and unreported. It has yet to be proved that these cinchophen compounds have any beneficial effect other than an analgesic one. The analgesic effect of external application has not been quantitatively compared with that of internal administration. The analgesic effect of drugs of the cinchophen group has not been compared with that of the salicylate group. It might be possible to elucidate the peculiar properties of the benzene ring when in combination with the hydroxyl group in substances ranging from the toxic and analgesic carbolic acid on the one hand through salicylic acid to the toxic and analgesic substances which are peculiarly injurious to the liver.

The following list of cinchophen derivatives, among others published in a recent number of the *Proceedings of the Staff Meetings of the Mayo Clinic*, is reproduced

in part so as to indicate to practitioners the particular drugs involved in the production of hepatic disease: Agotan, atochinol (atoquinol), atophan, atophanyl, biloptin (di-iodo-atophan), cinchophen (many brands), hexophan, neocinchophen, novatopan, phenylcinchoninic acid, phenoquam (phenoquin), quinophan, synthaline, tolysin.

The toxicity of chloroform, phosphorus, arsenic, and certain drugs of the salvarsan group is well recognized. The toxicity of the various preparations of cinchophen should be more extensively investigated. All cases presenting any clinical or laboratory signs of hepatic insufficiency should be analysed from the point of view of ingestion of toxic drugs and patent remedies.

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INTENSIVE VITAMIN THERAPY IN MEASLES

BY

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Recent research seems to have crystallized into the belief that vitamin A is concerned with raising the resistance of the animal body as a whole, and the epithelial cells in particular, to various bacterial invasions. The comparative scarcity of human investigations on this subject may perhaps be attributed to the fact that it is not easy to point to any clearly defined group of symptoms associated with a deficiency of this factor in man in any way analogous to the syndromes of rickets and scurvy. There is, however, good evidence for the belief that concentrates rich in vitamin A are valuable as prophylactics against infections.

VITAMIN A AND INFECTIONS

The work of Mellanby and his colleagues¹ on the prevention of puerperal sepsis by the use of such a concentrate appears convincing within the limitations imposed by the comparison of relatively small samples. There is, however, less evidence that a favourable influence can be exerted by such means on the course of a disease already in progress. The results achieved by Mellanby and Green² in the treatment (as opposed to prophylaxis) of puerperal infections await further confirmation. In Canada, Wright and his colleagues³ failed to protect a small series of babies against the "common cold" by supplying them with large amounts of vitamin A, while those contracting the disease did not appear to escape more lightly than the controls. Nevertheless, we are not entirely without indications to guide us in the search for a profitable field for vitamin therapy. In his classical experiments on the deficiency xerophthalmia of rats in 1922, Mori⁴ observed atrophy of the mucus-secreting cells in the salivary glands and in the mucous membrane of the larynx and trachea. If vitamin A was withheld for a further period, a local bacterial invasion of these tissues followed. Mori observed that most of his animals eventually died from bronchopneumonia. These findings were confirmed by Cramer and Kingsbury,⁵ and similar observations have been made by Steenbock,⁶ Mellanby,⁷ and others.