loss of sleep, a picture of severe fatigue is presented. The point that I want to make here is that the child will hardly ever complain of fatigue; this will be apparent in alterations in application and in behaviour. In other words, the first to have the opportunity of recognizing the onset of fatigue in a child will be the school teacher, and from this responsibility there is no escape.

The causes of fatigue may be in the child or in the school regime. Age is significant. I should say that children in pre-preparatory and preparatory schools are most prone to show fatigue by unsatisfactory behaviour and progress, although in girls fatigue may mar educational effort throughout school life. In boys, after a year or two at a public school, fatigue seems to lead more to illness than to nervous symptoms; by this time the boy has learnt to fend for himself and, be they masters or school-fellows, to persecute those who persecute him. Rapid growth in height is another strain on the child, and gives rise, also, I think, to diminished resistance to infections.

The liability to serious fatigue is greatly increased by any sort of subnormal physical health. Although it is not true to say that a child who is kept in good physical health will be free of physical and mental fatigue, yet there is an element of truth in the statement. Certainly the physical health of any child showing persistent symptoms of fatigue needs careful investigation. Some form of chronic toxæmia—often of obscure origin—may be at work, as, for example, disease of the tonsils or antra, disease of the bronchial glands, or, what is perhaps still more frequently found, toxæmia arising from the intestine, the condition which, in my view, is often falsely called "acidosis." Activity of the endocrine glands may also cause fatigue. Severe cases of fatigue are seen in adolescent girls, particularly just now in connexion with the prevailing habit of slimming. Many apparently alarming disorders of behaviour and thought at this age may mean nothing unduly serious.

The causes of fatigue attributable to school regime are numerous. I have already mentioned the choice of school and climate, and have discussed the question of diet and the great importance of ensuring that the child takes a proper quantity of food. The amount of rest provided is of the utmost importance. The hours devoted to sleep are mainly adequate, except, perhaps, in the upper forms at public schools. Rest, however, is not merely a matter of sleep. Nothing tries the nerves of some children more than the perpetual noise and rowing that may go on. Some period of silent rest, such as lying down with a book, should be ordered daily, and is often popular. Meals, too, should be taken in comparative quiet. It must be mentioned that summer-time means curtailed sleep for many children.

In my opinion the hours of work are far too long, and the harm that these long hours might do is only avoided by the slow pace which is set. The clever child learns to work slowly, and so spares itself, but the nervous child must work at high pressure, and thus may come badly to grief. Praiseworthy efforts are made in some schools to separate the quicker workers from the slower ones. From what I have heard, the Dalton system seems to make an effort to teach a child how to tackle its work and to take its own time over it. Some of our public schools for boys still lay themselves open to criticism concerning the activity they exact from the boys before breakfast.

Lastly, there is the difficult question of fatigue from examinations. When examinations are taken by children in their stride, as it were, they are harmless and useful; but public examinations, which have become competitive, are apt to be tests of a good memory and a smart coach.

Such examinations certainly put an immense strain on some children.

As regards the treatment of these tired children, the first essential is that the tired ones should be recognized, and I have already emphasized upon whom the responsibility for this must necessarily fall. The teacher must be able to distinguish between the actual fatigue and natural laziness, wilfulness, incompetence, or the results of fear. If in doubt the effect of a day or two in bed should be tried. Fatigue should be the first thing to occur to the mind to account for deterioration in work or character, and the doctor should be consulted on the possibility of a physical cause. For the rest it should be possible, especially in preparatory schools, to give the child an occasional day in bed, to provide extra rests and perhaps extra food, and to allow breakfast in bed; the latter does not seriously interfere with education, and it materially diminishes fatigue. It must always be remembered that a child has a natural tendency to right itself. I am sure that drastic alterations in its life, and evidence of concern in its psychology, should be avoided, and that the happiest results will be obtained by minor modifications of the school regime, friendly explanations, and sympathetic encouragement, all carried out quietly and with the lightest of touches.

MODERN VIEWS ON THE MECHANISM OF GALL-STONE FORMATION

BY

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Gall-stones are a common cause of pain and disability, and therefore a considerable amount of work has been done to determine the causes of their formation and the best methods of treatment. The subject has been investigated from various angles—clinical, morbid anatomical, bacteriological, biochemical, and experimental—and much of the work is scattered about in various types of journal and not readily available to the general reader. A brief review of modern views on gall-stone formation may therefore be of interest.

THE FACTOR OF INFECTION

The first difficulty that arises is the definition of "modern," and how new a view has to be for inclusion in that term. In this article an attempt will be made to get over that difficulty by first of all giving Naunyn's classical theory of gall-stone formation, and then discussing in what ways our views have had to be modified as a result of increasing knowledge. Although this theory dates from the last century, it was widely accepted in its entirety as the best explanation of the formation of gall-stones until a comparatively few years ago. According to Naunyn, the essential factor in the formation of all gall-stones was infection, the usual infecting organisms being of intestinal origin. These organisms acted on the wall of the gall-bladder and gave rise to a "lithogenous catarrh," as a result of which cholesterol was formed by the gall-bladder wall and shed into the lumen of the gall-bladder, together with small quantities of calcium and organic matter. If in sufficient concentration, these substances in the presence of stasis combined with the pigments of the bile to form a calculus. As a result of secondary cholesterolization of a primary mixed calculus, it was postulated that eventually a pure cholesterol calculus might be produced. Naunyn appreciated that gall-stones were commoner in

women than in men, and attributed this to the greater tendency to biliary stasis in women from the less strenuous character of their occupation, the wearing of tight-fitting corsets, and the bearing of children.

Thus the corner-stone of Naunyn's theory was infection, but opinions on the aetiological importance of this factor have varied widely since Naunyn's day. One of the earliest and most persistent opponents of the Naunyn theory was Rovsing, a Scandinavian surgeon, who based his opinion on the frequency with which in a large personal series of gall-stones removed at operation no organisms could be found. He held the view that, when organisms were to be found in gall-stones, they were to be regarded as secondary invaders. Unfortunately, Rovsing had no bacteriological investigations made of the gall-bladder wall, which we now know is frequently infected when the contained stones are sterile. Meanwhile, the possible importance of metabolic factors in the formation of gall-stones began to be realized, particularly by Chauffard and his pupils in France. Aschoff, approaching the subject particularly from the morbid anatomical standpoint, attempted to reconcile conflicting views by describing two types of gall-stones, one formed as the result of pure metabolic factors, the other as the result of infection. The trend of opinion was away from the simple direct-infection-gall-stone relation as postulated by Naunyn, when in 1916 Rosenow of the Mayo Clinic swung right back again and claimed to find in human gall-stones certain specific streptococci which on injection into animals tended to localize electively in the gall-bladder and produce gall-stones. Rosenow's work has been widely quoted, but by other workers his findings were not confirmed and his views had not won general acceptance when in 1927 A. L. Wilkie, working in the School of Experimental Surgery at Edinburgh, claimed to have produced similar results. By both Wilkie and Rosenow the important organisms in gall-bladder disease were thought to be not intestinal organisms, as had always previously been held, but organisms from peripherally situated foci, such as the teeth or tonsils. Wilkie's work has been strongly criticized, however (Williams and McLachlan), and has not been confirmed.

It is thus impossible at present to give any dogmatic or final conclusions on the relation between infection and gall-stones. The general opinion is, however, that there is some relation between infection and gall-stones, since the gall-bladder wall is infected in approximately 70 per cent. of cases of gall-stones, the fluid contents in 40 per cent., and the gall-stones themselves in 30 per cent. (Gordon-Taylor and Whitby—collected statistics). Moreover, it is widely accepted in opposition to A. L. Wilkie and Rosenow that the common infecting organisms are intestinal—*B. coli*, *B. welchii*, *Streptococcus faecalis*, and *B. typhosus*. But there is very little substantial evidence on which it can be determined whether the infection is primary or secondary, or the way in which it normally reaches the gall-bladder. And although it is generally believed that infection is an important aetiological factor in at any rate some types of gall-stones, the modern view is that it is probably not the simple direct relation that Naunyn postulated, but a more complex combination of factors involving alterations in the normal physiological absorptive powers of the gall-bladder mucosa and the chemistry of the bile. One recent article may be quoted to illustrate this point. Andrews and his collaborators state that if the gall-bladder is inflamed it not only absorbs water as Rous and McMaster had previously shown, but also bile acids. It is the bile acids that are chiefly responsible for keeping cholesterol in solution in the bile, so that their diminution would predispose to the precipitation of cholesterol. If this finding of Andrews is con-

firmed, a very important way in which infection may predispose to gall-stones will have been demonstrated.

METABOLIC FACTORS

The possible importance of metabolic factors in gall-stone formation has been extensively investigated by modern workers. In Naunyn's day the chemical tests for cholesterol and other constituents of gall-stones were so crude that practically nothing was known of their metabolism. To-day, though there are still large gaps, our knowledge has been considerably extended. It is known, for example, that even the common mixed gall-stones are composed predominantly of cholesterol, which constitutes anything from 80 to 98 per cent. of the calculus (Peel); that cholesterol may be present in the gall-bladder bile in concentrations of anything from 100 to between 800 and 900 mg. per 100 c.cm. (Peel); that it is present in the blood plasma of normal individuals in anything from 80 to 220 mg. per 100 c.cm., with an average of 153 mg. per 100 c.cm. for females and 170 for males (Gardner); that in certain conditions (for example, parenchymatous nephritis, jaundice, pregnancy, diabetes) the amount of cholesterol in the plasma may be increased; and that this increase may be associated with an increase of cholesterol in the bile excreted by the liver, though the last statement is still disputed. Chauffard has attempted to relate hypercholesterolaemia directly with gall-stones. Thus he states that there is a hypercholesterolaemia of pregnancy which is probably related to the relative frequency of gall-stones in women, and also in the convalescence from typhoid fever, which he thinks may be a factor in the occasional development of gall-stones after this disease. Gardner and Gainsborough, however, have shown that hypercholesterolaemia is not a constant occurrence in pregnancy, though the relation between the amounts of free cholesterol and cholesterol esters in the blood is usually altered. Chauffard also stated that gall-stones are usually associated with hypercholesterolaemia, but it has been shown that this only occurs when the stones are causing obstructive jaundice (Gardner). Gardner has also shown that a condition such as subacute parenchymatous nephritis, which is associated with a marked degree of hypercholesterolaemia, shows no special tendency to be associated with gall-stones. Attempts to correlate directly the amount of cholesterol in the blood with gall-stones have thus failed, and it is probable that before further advance can be made on these lines more will have to be known of the precise place of cholesterol in the metabolism of the body. But that the amount of cholesterol in the bile is of fundamental importance in the formation of gall-stones is strongly suggested by the fact that gall-stones formed predominantly of cholesterol are confined to man, and that in animals, which have a much lower cholesterol content of the bile, cholesterol gall-stones of the type found in man have never been found naturally, nor, with rare exceptions which will not bear critical analysis, have they been produced experimentally. In fact, Naunyn was one of the first to point out that human gall-stones may become dissolved if placed in the gall-bladders of animals.

As regards other metabolic factors, much attention has been directed to the bile acids and their salts, which are responsible for the keeping of cholesterol in solution in the bile. Chemically, the bile acids appear to be closely related to cholesterol (Gardner). Smyth and Whipple found that the amount of bile acids excreted in the bile of dogs was markedly diminished as the result of quite small doses of chloroform and increased after meat feeds. The drugs tested (atropine, pilocarpine, quinine, calomel, sodium salicylate, and alcohol) had no marked effect either way. Andrews and his collaborators

found that if the ratio of bile acids to cholesterol falls below 13 precipitation of cholesterol begins. In human bile the bile acid-cholesterol ratio is normally in the neighbourhood of 20 or 30, which is dangerously near the critical point. In animals, on the other hand, owing to the lower cholesterol content of the bile, the ratio is nearer 100, so that the failure of cholesterol stones to be formed in animals is not surprising. This difference between the constitution of human and animal bile is one of the greatest difficulties in the way of experimental investigation of the subject and in the interpretation of experimental results.

In addition, the factors responsible for variations in the pigment of the bile have been studied. Bile pigment is chemically closely related to the blood pigments, and it is well recognized that in acholuric jaundice, in which there is excessive haemolysis, there is a special liability to pigment calculi. Rovsing, following Boysen, went so far as to regard all gall-stones as primarily due to a breakdown in pigment metabolism with the production of pigment nuclei on which cholesterol became deposited; but this is not generally accepted.

It would therefore seem that at present a study of the metabolic factors in gall-stone formation and the possible influence of local infective conditions of the biliary tract on these factors offers a hopeful line of approach to the gall-stone problem.

The chief surgical contribution to the pathology of gall-stone formation in the last twenty years or so has been the discovery of the "strawberry gall-bladder" or "cholesterolosis gall-bladder." This is the condition in which deposits of cholesterol are found in the mucosa either as whitish streaks or polypoid masses. The history of strawberry gall-bladder has recently been reviewed by Elman and Graham, and by Illingworth. They state that the condition was first described by Moynihan in 1909, the term "strawberry" being coined by MacCarty a year later. Illingworth found that out of a large number of gall-bladders removed surgically at the Edinburgh Royal Infirmary one-fifth showed these deposits in the mucosa in greater or lesser degree. Sometimes they occur in otherwise normal gall-bladders, sometimes in inflamed gall-bladders, and sometimes in association with gall-stones. Precisely how the cholesterol gets into the mucosa of the gall-bladder is not decided. By some it is believed to be absorbed from the bile (Boyd, Illingworth), by others to be in process of excretion into the gall-bladder (Elman and Graham). At present strawberry gall-bladder affords an important field of study for the aetiology of gall-stones.

OTHER FACTORS CONSIDERED

Stasis of bile was thought by Naunyn to play an important part in the formation of gall-stones, and he considered in detail the various factors, such as lack of exercise and tight lacing, which were believed to predispose to stasis. But the increased knowledge gained from the modern x-ray test of cholecystography has led to considerable alterations in old ideas of how the gall-bladder emptied. Whitaker showed that the cause of emptying was a contraction of the musculature of the gall-bladder, and that extrinsic factors such as respiration played little or no part. It is now known that the ingestion of different kinds of foodstuffs affects the emptying of the gall-bladder in different ways, most potent in causing the gall-bladder to contract being fatty foods. And the giving of a fatty meal is to-day a routine part of the test of cholecystography. Westphal and his co-workers lay considerable stress on the importance of functional disorders of motility of the gall-bladder and biliary passages. According to them, stasis in the gall-bladder may result either from hypo-

tonicity of the gall-bladder itself or from hypertonicity of the sphincter mechanisms. They believe that stasis thus produced plays an important part in the production of gall-stones. As regards pregnancy, since Naunyn's day this has commonly been believed to be the important factor accounting for the well-recognized greater frequency of gall-stones in women, one of the ways in which it was presumed to act being by the production of biliary stasis. But Gross in 1931 published an analysis of a large number of cases of gall-stones from the post-mortem records of the Leeds General Infirmary, and though she found in accordance with general experience that the condition was twice as frequent in women as in men, when the proportion of married to single women admitted to the hospital was taken into account the married women were no more liable than the single. If Gross's figures are confirmed, then some factor other than pregnancy will have to be discovered to explain the greater liability of women to gall-stones. It is thus interesting that the three chief factors postulated by Naunyn as predisposing to stasis of bile—namely, lack of exercise, tight lacing, and pregnancy—are all open to serious criticism in the light of modern knowledge.

That vitamin deficiency might be a factor in the formation of gall-stones was almost bound to be suggested in view of the rapidly growing importance of these accessory food factors, but the evidence is very slender. It is based on some experimental work by Fujimaki, who found that rats fed for prolonged periods on diets deficient in vitamin A developed among other things small concretions in the biliary tract. There is no detailed analysis of these concretions, and they do not seem to correspond to human gall-stones. Clinical evidence, too, is against gall-stones being a deficiency disease, as also is the fact that cholesterol gall-stones appear to be more common in the more variedly and richly fed peoples of Western civilization than in the East (Miyake, Digby).

Finally, mention must be made of the work of Lichtwitz, Schade, and others on the physico-chemical aspects of gall-stone formation. Schade states that all attempts to explain biliary and urinary calculi on simple laws of solution have failed, one important reason being the presence of colloids in body fluids which increase the stability of the solution. He also points out that the structure of the various concretions formed in the body does not correspond with that of crystals of the same substances formed in a test tube. The pure cholesterol calculus, he states, is due to the precipitation of cholesterol from a supersaturated solution, but it is a special type of precipitation, resulting from the presence of small amounts of fatty substances in the bile. The common cholesterol-pigment gall-stone, on the other hand, he believes is inflammatory in origin, the inflammation resulting in the presence of an appreciable amount of irreversible colloid in the gall-bladder, which acts as a binding material for the crystalloid elements. The fact that these inflammatory gall-stones are usually multiple he attributes to the formation of numerous calcium-albumin adsorption points as the result of the inflammation. Schade's conclusions from his chemical studies thus resemble those of Aschoff, who, from morbid anatomical considerations, believed in a different causation for the crystalline cholesterol gall-stone and the common mixed stone. We have little knowledge of the time period required for the formation of the usual human gall-stone, although the structural similarity of different gall-stones from the same case makes it almost certain that they are as a rule formed at the same time. If any surgeons, therefore, have had the experience of finding gall-stones in a gall-bladder which has been noted at a previous operation to be devoid of stones, their observations would be of value on this point.

GENERAL SUMMARY

To summarize, therefore, increasing knowledge has made it obvious that the comparatively simple explanations of gall-stone formation of some years back no longer hold, but as yet no completely satisfactory alternative explanation has been brought forward. Many factors appear to be involved in gall-stone formation, and it is not yet possible to evaluate their precise position in causation. But in spite of this it is true to say that a real increase of knowledge and a clarification of ideas has taken place. On the statistical side the most striking contribution is that of Gross, especially her conclusion that married women are no more liable than single to gall-stones. The bacteriology of gall-stones has been carefully worked out, and the frequency with which the gall-bladder wall is infected as compared with the gall-stones themselves is generally noted. The view that there are certain types of streptococci with an elective affinity for the gall-bladder has not won general acceptance, but anaerobic organisms have been shown to be not infrequent invaders (Gordon-Taylor and Whitby). It is on the biochemical aspect that the biggest advances have been made, and this possibly affords the most promising line of investigation at the moment, the metabolism of cholesterol, the question whether the gall-bladder absorbs or secretes cholesterol, the factors responsible for the varying amounts of bile acids and cholesterol secreted in the bile by the liver, and the effect of inflammatory and other lesions of the liver and biliary passages on these substances all being of great importance in this connexion. Schade's work on concretions as a problem in physical chemistry is interesting, and, although his conclusions are disputed, it is a line of work that merits further exploration.

Finally, the question of course arises whether the increase of knowledge that has taken place has any practical application. From the point of view of diagnosis there is no doubt that the modern x-ray test of cholecystography (Graham) has within the last decade revolutionized the clinical recognition of gall-stones. But from the point of view of treatment the patient with gall-stones has still only two alternatives—to keep them with any trouble they may be causing, or to have them removed by a surgical operation. Because, therefore, of the predominant position that surgery occupies to-day in the treatment of gall-stones, the surgeon's position is a particularly responsible one, and, although many of the problems may lie outside his immediate interests, he may yet do much to initiate work which will lead to an increased knowledge of gall-stone formation and advances in treatment along all lines.

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THE AETIOLOGY AND TREATMENT OF PERNICIOUS ANAEMIA

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Just a quarter of a century ago I put forward in this *Journal*¹ a theory, which was at that time new and heterodox, of the aetiology of pernicious anaemia. Various and discordant views were then held as to the causation of this disease—that it was due to a toxic haemolysis, to repeated small capillary haemorrhages, to a specific infection of the alimentary tract, to a protozoal infection. I suggested that it might be a deficiency disease due to "a deficient available quantity of those materials which go to form the stroma of the red blood corpuscles." This hypothesis was ignored or scouted at the time, but it seems that opinion has in recent years veered round to it. As my original argument was relatively concise, it may be worth restatement exactly as it was given.

"A THEORY OF THE BLOOD DEFECT IN PERNICIOUS ANAEMIA"

"The aetiology of idiopathic or pernicious anaemia is still obscure, and therapeutic measures are correspondingly inadequate to combat the disease. In these circumstances any reasonable suggestion bearing on its pathology or treatment may have some value. Pernicious anaemia in regard to blood abnormality is characterized especially by a great diminution in the number, with generally a high individual haemoglobin value, of the red blood corpuscles. It presents in this respect a striking contrast to simple anaemia, in which disease, while the number of the red blood corpuscles is not conspicuously lessened, each individual erythrocyte is markedly poorer in haemoglobin than are the red cells of healthy blood. In the case of simple anaemia, though the ultimate aetiology of it may be debated, this at least is generally accepted, that there is for some reason a deficient supply to the blood-forming organs of material available for making haemoglobin, and that this defect of material can be made good by the therapeutic administration of iron. The facts that in pernicious anaemia there is found abundance of iron in the liver and in other organs, and that iron is useless as a remedy, would seem to show that in this disease the defect does not lie in the haemoglobin factor of the corpuscles. Moreover, each erythrocyte contains in many cases a quantity of haemoglobin in excess of that which is found in the erythrocytes of healthy blood. May the defect not lie in the other constituent of the red cell—the stroma? There may be supplied to the blood-forming organs in a patient suffering from pernicious anaemia a deficient available quantity of those materials which go to form the stroma of the red blood corpuscles. There is present, as it were, in the body haemoglobin enough, but not enough material for stroma in which the haemoglobin may find place. The stroma of the red blood corpuscles consists largely of lecithin and cholesterol. The condition known as pernicious anaemia may be due to a deficiency in the body of lecithin or cholesterol, and the administration of these substances may be of some use as a remedy. Certain facts go to show that there may be some defect in the stroma of the red cells in this disease. For example, they do not run into rouleaux in normal fashion. It has