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

BY

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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

been shown that bodies suspended in a watery solution run into rouleaux only when possessed of a fatty covering. The absence of this phenomenon in pernicious anaemia may be due to a defect in the stroma of the red blood corpuscles, in the lecithin and cholesterin elements, which though not true fats are yet of a fatty nature. The condition of poikilocytosis and abnormal staining of the red cells, sometimes present in pernicious anaemia, may be due partly to the same defect. On such a hypothesis of the blood defect in pernicious anaemia, the results of its somewhat empirical treatment may possibly be explained. The giving of bone marrow recommended by Fraser may be merely a method of supplying to the blood-forming organs those constituents of stromae which they lack. Lecithin is certainly known to exist naturally in the bone marrow. Arsenic, which, since its introduction by Byrom Bramwell in this disease, has been found to benefit a certain number of cases, may act on the stroma of the red blood corpuscles in such a way as to remedy this defect and increase their resistance. Indeed, lecithin has been found to increase the number of the red cells, and some experiments which I have made with regard to the action of arsenic on these cells have gone to show that it increases their resisting power. Nor is there any inherent reason, if a deficiency of iron, for example, or of calcium can cause morbid conditions, why disease may not also be set up by a lack of such necessary constituents as lecithin or cholesterin."

The main contention was that pernicious anaemia is due to a lack of "those materials which go to form the stroma of the red blood corpuscles." Not only this conclusion, but the premisses upon which it was based, seem to resemble very closely those which have later been admitted. For example, Whipple² wrote in 1922:

"Our conception of pernicious anaemia is that there is a scarcity of stroma-building material or a disease of the stroma-forming cells of the marrow which limits the output of red cell framework. There is plenty of pigment material (an excess in fact) as evidenced by the high colour index or the saturation of the red cells with haemoglobin."

It is unnecessary here to attempt to recapitulate the recent advances in knowledge of pernicious anaemia, which furnish one of the most brilliant successes of therapeutics. The value of liver diet and of liver extracts has been firmly established. As to what the substance is which, occurring in various organs, seems to supply the material lacking for stroma formation, there is still doubt—a doubt which may soon be dispelled. There is a good deal of evidence to show that more than one substance, and possibly not always the same substance, may be lacking. My original conjecture that the failure to produce red cells in pernicious anaemia might be due specifically to lack of lipid material seems to have been disproved. At any rate, this cannot be the sole factor, so far as one can judge from the evidence of liver extracts.

A SUGGESTION PUT FORWARD

My object in publishing this note is, however, not to derive a melancholy satisfaction from the fact that I was nearer the mark than the authorities of my early days were willing to allow, but to make a further suggestion. As Whipple says in the paper already quoted: "hypotheses are of some value for further work, even if there be little or no truth in them." Having formulated this hypothesis of the causative factor in pernicious anaemia, I attempted in 1908 to proceed to the next obvious step, which was to administer the separated stroma material in pernicious anaemia. I tried to obtain this by haemolysing defibrinated ox blood and separating the stroma by centrifuging. Having at my disposal only a very small centrifuge, I obtained only an insignificant amount of stroma material. Having also no facilities for testing this material clinically, even if I could obtain a sufficient quantity of it, and

having little hope of persuading anyone to test the fruits of a discredited hypothesis, I gave up the work, discouraged. During recent years, when opinion has come round in the direction of believing that pernicious anaemia is due to some lack of stroma-forming substance, I have wondered that no one has done the experiment I originally contemplated, and which still seems to me a crucial experiment. It may have been done and escaped my notice. In the belief that it has not been tried, I venture to put forward the following considerations in the hope that someone who has the requisite plant and facilities will hazard the gamble.

If pernicious anaemia is due, partly or wholly, to a lack of the materials (in the widest sense) necessary for stroma formation, it would seem that the most direct and complete method of supplying this deficiency would be to administer the actual stroma material as a whole and unchanged. Presumably all the materials necessary for the ultimate stages of stroma formation are there present. As it is impossible to foretell to what extent, if any, the stroma constituents may be destroyed by digestion, a saline suspension of stroma might first be tried intramuscularly. It is more than probable that, if this were to be effective at all, it would act quickly in pernicious anaemia.

If it did act, it might be easier to obtain the active principle from stroma material than from liver or other organs, because the chemical structure of the stroma must almost certainly be less complicated than that of liver. The stroma is only a box, while the liver has many functions to perform other than those concerned with blood metabolism. It is possible, however, that, even if the supposition be correct (that pernicious anaemia is due to lack of stroma-building material), the administration of completed stroma material will not supply the deficiency, because the blood-forming organs may deal with the precursors of that material and may not be able to avail themselves of the material in the full and final stage of its synthesis. This possibility is, however, not sufficiently deterrent to oust the propriety of trying the administration of stroma material in pernicious anaemia. If this proved successful, it might provide a therapeutic agent, cheaper and more concentrated than liver extract, it might furnish a simpler matrix for extracting the active principle, and it would certainly provide further direct evidence as to the aetiology of pernicious anaemia.

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CRYPTO-EMPYEMA

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By crypto-empyema is meant an empyema that cannot be diagnosed by repeated needling, even under an anaesthetic. The term is useful, if for no other reason than that it reminds the practitioner that empyema ought to be diagnosed and treated, on occasion, when pus cannot be found by the exploring needle.

Three cases of this condition that have come under my care may be briefly related.

CASE I

A public school boy developed a left empyema nine days after the onset of pneumonia. Temperature was 103°, pulse 100, respirations 30. A large empyema was evacuated by rib resection after locating the pus with a needle. It contained streptococci and saprophytes. For a few days he did well, then the temperature rose again, and the boy looked