I am glad to see that Emil Novak¹³ in a recent paper agrees with my view of the periodicity of the human menstrual cycle. These are his words:

"In reference to Wagner's views on the primacy of the corpus luteum, provocative as Wagner's study is, it makes one wonder whether we are not chasing a will-o'-the-wisp, for beyond the corpus luteum looms the pituitary, and perhaps beyond the latter we shall have to fall back on some innate periodic human factor as elusive as the life principle itself."

REFERENCES.

- ¹ Parkes, A. S.: *The Internal Secretions of the Ovary*.
- ² Johnstone, R. W.: *Amer. Journ. Obstet. and Gynecol.*, February, 1930.
- ³ Hammond: *Reproduction in the Rabbit*, Edinburgh, 1925.
- ⁴ Gerlinger: *Le Cycle Sexuel chez la femelle des Mammifères*, Strasbourg, 1925.
- ⁵ Corner: *Cyclic Changes in the Ovaries and Uterus of the Sow and their Relation to the Mechanism of Implantation*.
- ⁶ Allen: *Embryology*, 1927, 19.
- ⁷ Whitehouse: *Lancet*, June 18th, 1927.
- ⁸ Hartman: *Amer. Journ. Obstet. and Gynecol.*, April, 1930.
- ⁹ Zondek: *Arch. f. Gynäk.*, 1927, 132.
- ¹⁰ Evans: *The Function of the Anterior Hypophysis*, Harvey Lectures, 1924.
- ¹¹ Cannon: *Irish Journ. Med. Sci.*, January, 1930.
- ¹² Wagner: *Zentralbl. f. Gynäk.*, January 7th, 1928.
- ¹³ Novak: *Journ. Amer. Med. Assoc.*, March 22nd, 1930.

SUBACUTE COMBINED DEGENERATION OF THE CORD IN PRIMARY ANAEMIA OF THE FOWL:

ITS PATHOGENESIS AND THAT OF ASSOCIATED LESIONS.

BY

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(With Special Plate.)

In a previous communication¹ subacute combined degeneration of the cord was described as occurring in fowls with primary or pernicious anaemia. This subject is of such importance to an understanding of pernicious anaemia and its nervous complications in the human being that the condition has been taken up again for more detailed discussion in the present paper.

During the past four years seven such cases have been recognized and observed in some detail. Their essential nature was first suspected when, post mortem, the milk-chocolate-coloured liver, small in size, was found present. This, indicative of the presence of haemosiderosis, is one of the most characteristic findings in primary anaemia of the fowl. A description of the cases in question will now be given.

CASE I.

Hen 104. White Leghorn, 1 year old, has been ill for some time, lying about on its side. When approached it tries to escape, but staggers and at once tumbles on to its side again; mentally it is quite alert. It died before any extended examination of its blood was made. The haemoglobin, however, was 60 per cent., while a blood film showed a fair degree of erythroblastosis.

Post mortem it was found to be very emaciated. Naked eye, no obvious lesion was seen except that the liver, spleen, and kidney were exceptionally small in size, and that the liver showed the "milk-chocolate" hue. The femur and tibia were filled with an abnormal marrow, which resembled blood in its colour and consistence; while the metatarsal bone was exceptional in that the fat there, instead of being pure yellow in colour, was of a reddish tint.

Microscopic examination disclosed a marked haemosiderosis in the liver, spleen, and kidney; in the latter, especially of the secreting tubules. The occurrence in this latter situation is to be emphasized because, in my experience, this has been found associated only with haemolytic conditions, and has not been observed to occur otherwise, as, for instance, in feeding experiments with large doses of iron salts. Its occurrence, together with the appearances in the liver and spleen, in cases like the present one, is regarded as strong evidence of a primary anaemic condition, existing behind the more obvious nervous implication.

The marrow showed the appearances one finds in a primary anaemia—namely, a haemocyto-blastic hyperplasia and entire absence of fat cells. The lower dorsal region and the lumbar enlargement of the spinal cord were treated by Marchi's method. Sections prepared from these situations showed in both, but especially in the dorsal region, degeneration of the white matter in the posterior and antero-lateral columns of the cord. There was no neuroglial proliferation or sclerosis.

CASE II.

Hen 105. White Leghorn, 1 year old, has been lying about for some time; quite alert, but shows a weakness of the right leg. Haemoglobin is 70 per cent. (normal for fowl); blood films show slight changes only, of the nature of anisocytosis; no erythroblasts seen.

The conditions found, post mortem, and microscopically in the liver, spleen, and kidney, especially as regards haemosiderosis, and in the marrow, were as in hen 104. The cord in the dorsal and lumbar regions showed similar degenerative changes.

CASE III.

Hen 107. Light Sussex, 3 years old, paralysed in both legs and unable to stand. Haemoglobin is 70 per cent., red blood cells 2,000,000 per c.mm., while the blood films show nothing distinctively abnormal.

Post mortem, the conditions present were much as in the previous cases. This hen, however, was very fat. The femur and tibia were greatly sclerosed and thickened, resulting in a great diminution in the quantity of marrow. This was of a pale colour, and looked like dirty tallow.

Microscopically the liver, spleen, and kidney, especially as regards haemosiderosis, resembled previous cases. Here, however, the marrow was of a very fatty aplastic nature, there being very little evidence of any haematopoietic activity, and it was greatly reduced in quantity owing to the bone sclerosis.

The cord in the dorsal and lumbar regions was more markedly involved than in the previous cases. The same columns as previously were affected with the degenerative process. Fig. 1 shows the condition in the lumbar enlargement, degeneration being especially noticeable in the posterior columns.

CASE IV.

Hen 121. White Leghorn, 1 year old, unable to walk. When it tries to do so it tumbles over on to its side. Haemoglobin is 70 per cent., while the blood films show nothing abnormal. The conditions found post mortem were as usual. The omentum, however, contained a great quantity of fat; the fowl was not emaciated. The marrow in the femur and tibia was of a pale grey colour, and quite abnormal.

Microscopically the appearances in the liver, spleen, and kidney, especially as regards haemosiderosis, were as in previous cases. The marrow was aplastic and fatty, and showed very little active haematopoiesis. Very marked degenerative changes similar to those already described were found in the dorsal and lumbar regions of the cord.

CASE V.

Hen 122. White Leghorn, 1 year old, showed considerable weakness in the legs, but not so marked as some of the others. Haemoglobin was 60 per cent., while the blood films showed nothing markedly abnormal. Post mortem the usual conditions were found, including the milk-chocolate-coloured liver. There was great emaciation. The marrow in the femur and tibia was crimson and very fluid, resembling thin red-currant jelly.

Microscopically the liver, spleen, and kidney were as usual, the haemosiderotic condition being marked. The marrow showed great congestion of numerous blood sinuses, which had replaced the usual fat cells and functioning marrow tissue. The changes in the dorsal and lumbar cord were as in hen 121, only not so marked.

CASE VI.

Hen 223. White Leghorn, 1 year old, paralysed and unable to stand. The haemoglobin was 40 per cent., while the red blood cells numbered 845,000 per c.mm. Blood films showed marked erythroblastic changes.

Post mortem the conditions found were as in previous cases. This hen, however, was not emaciated. By this time one had come to appreciate the importance of the duodenum in relation to the excretion of iron in primary anaemia,² and the duodenal mucosa in this case was found to be deep rusty brown in colour. The femur and tibia were very markedly sclerosed, while the greatly diminished marrow was quite abnormal in appearance, being of a pale grey colour.

Microscopically the appearances in the liver, spleen, and kidney were as in the previous cases, including the haemosiderosis. The duodenal villi showed considerable iron pigment in their cores. The marrow was very definitely aplastic. The dorsal and lumbar cord showed the usual lesions.

CASE VII.

Hen 360. White Leghorn, 2 years old, can walk about and even run, but every now and then, without warning, it falls backwards and sits down. It lies in the house all day, and does not mingle with the other hens in the run. The haemoglobin was 70 per cent., and red blood cell count 2,100,000 per c.mm. Blood films showed nothing markedly abnormal.

The conditions found post mortem were as usual, including the typical liver appearances. The mucosa of the duodenum was slightly less brown than in hen 223. The femur and tibia showed

great sclerosis, and the marrow was considerably diminished in quantity. It was of a reddish colour.

Microscopically the appearances in the liver, spleen, and kidney were as usual, including the haemosiderosis. The marrow showed absence of fat cells and great increase in number and distension of the venous sinuses, with consequent diminution of the haematopoietic tissue. Sections of the lumbar and dorsal cord showed very marked degeneration in the usual situations. The condition present in the dorsal cord is shown in Fig. 2.

The important findings derived from these observations may be summarized. In a series of fowls, lesions of the cord, indistinguishable from those described as occurring in subacute combined degeneration of the cord in human beings, have been found. In all the cases this has been associated with the existence of a high degree of haemosiderosis of the liver, spleen, and kidney, and also of the mucosa of the duodenum, where this was examined. In three cases there was also very marked sclerosis of the bones, with great diminution in the quantity and marked change in the appearance of the marrow. The marrow, when examined microscopically, has been found to be abnormal in all the cases. In some it showed atrophy or aplasia; in others considerable diminution, accompanied by great increase and distension of the venous sinuses; while in others it showed a haemocytoelastic hypertrophy, such as one finds typically in active pernicious anaemia of the fowl. In some of the cases there was comparatively little alteration in the circulating blood. In one case, however, there was considerable reduction in the haemoglobin percentage and number of red blood cells, while in others there was evidence of blood instability, as shown by the presence of erythroblasts.

Attention may also be drawn to a further circumstance. It will be seen that most of the cases in the present series are in young fowls of about a year old. Further, that in the older cases sclerosis of the bones becomes a more marked feature. These occurrences are exactly paralleled by what takes place in the pure primary anaemia of the fowl without nervous complications. This circumstance suggests the essential identity of the two conditions.

The significance of the occurrence of the paralytic symptoms in fowls, the circulating blood of which seemed in most cases to be fairly normal for the time being, requires discussion at the outset. In the routine of the poultry industry a fowl is rarely noticed to be anaemic or to have a yellowish comb until the haemoglobin has fallen to about 35 per cent.* It may be mentioned, however, that yellowness of the comb is not a function of the haemoglobin content of the blood alone. It is determined also by the strength of the circulation, which, even if the blood has a low haemoglobin content, may suffice to keep the cavernous sinuses of the comb sufficiently full of blood to hide the normal yellow coloration of the tissues due to carotene or xanthophyll,† and thus produce a reddish coloration. There is room, obviously, for exceptions to the above rule, which, however, is not submitted as being infallible.

In general, therefore, in fowls, there occurs a zone of haemoglobin deficiency between 70 per cent. (normal) and 35 per cent., within the limits of which the fowl may not be discovered in practice to be ailing at all, or specifically to be suffering from an anaemia. For long periods, therefore, with relapse and remission, it is possible that fowls may be affected with a severe anaemia without this being appreciated. In the present series, for instance, in the majority of the cases there was no history of previous illness or of the occurrence of anaemia. Another aspect of the same subject is the fact that in routine practice fowls with anaemia of gravity indicated by 20 per cent. haemoglobin and 400,000 red blood cells per c.mm. may be regarded as having been just taken ill, when further examination shows them to have very old-standing disease in a relapse stage after a long remission.

* Observations made on a considerable number of "healthy" hens, which showed no outward signs of anaemia, have disclosed in several cases not only haemoglobin and red blood cell deficit, but, more important from the point of view of the present discussion, marked haemosiderosis and considerable marrow changes.

† Yellowness of the comb and other body tissues, especially the fat, is a very frequent occurrence in primary anaemia. This is not due to bilirubin, but to carotenoid pigments which are unoxidized and so accumulate (vide Rummo, *Rif. Med.*, 1930, January 30th, p. 96; also Bedson and Knight, *Journ. Path. and Bact.*, 1924, 27, p. 239).

That in the paralysed fowls of this series there has been a state of anaemia, associated with haemolysis, is amply evidenced by the haemosiderosis, and that it has been of comparatively long duration is shown by the state of the marrow and the advanced sclerosis of the bones. How the circulating blood happens to be normal, more or less, when these cases are first observed, and what bearing these points have on an understanding of the human disease, will be discussed shortly.

Before going on to the general discussion the ground may be further cleared by referring to some points which, apparently axiomatic, are nevertheless liable to be overlooked. An organ or tissue may be damaged, so far as the influence on it of its blood supply is concerned, either from normal blood being supplied to it in insufficient quantity (owing, perhaps, to the supply vessels being constricted or to the blood pressure being low), or from blood, abnormal in cell and haemoglobin content, being supplied in the normal quantity, or even in deficient quantity, owing to weakness of the heart and low blood pressure—occurrences very common in anaemic conditions. These considerations have an important bearing on an understanding of the changes occurring in certain organs—for example, the nervous system, stomach, etc.—as will be discussed later on.

Collier,³ in dealing with subacute combined degeneration of the spinal cord, mentions as a synonymous designation for the condition "the anaemic spinal disease." This in itself will serve to show how closely this disease has been associated in some minds with anaemia. He states, further, that the early writers believed that the anaemia was the essential part of the disease, and that the degenerations in the nervous system were the result of vascular changes* consequent on the anaemia. He goes on to mention that this view is negated by the fact that some cases progress to a fatal issue without any evidence of anaemia. As has just been pointed out, however, anoxaemia of a part may be due to lack of blood as a whole rather than to a deficit of haemoglobin and red blood cells in the blood. In this regard it may be mentioned that Kattiwinkle (quoted by Collier) considers that the primary spots of degeneration in the cord in this disease are determined by the vascular distribution, and that they result from disease of the perivascular lymphatics. Again, Osler and McCrae,⁴ while arguing for a toxic origin of the disease, point out that the action of the toxin on the nervous system affects first, as one would expect, those tracts whose mere length must necessitate a more elaborate nutrition for their maintenance. It is obvious that the long tracts would be at least equally liable to damage owing to the difficulties of blood supply, especially in conditions of anaemia, where not only is the blood poor in quality, but the quantity deficient, owing to the weakness of the heart and the lowered blood pressure.

It may be that the cases of subacute combined degeneration of the cord associated with pernicious anaemia do not constitute all the possible cases of this disease. There may be others due to mechanical anoxaemia, and these might theoretically constitute the cases referred to by Collier as being unassociated with anaemia. Another more likely possibility will be discussed immediately.

Following his original argument, Collier proceeds to state, as evidence against an anaemic causation, that in other cases the nervous manifestations may become severe long before any anaemia is present. The possibility that anaemia of sufficient degree to be damaging may have been present previously, but unobserved, in such cases is not discussed. Such a contingency, we have shown, cannot be overlooked in fowls. Parallel events, moreover, occur in pernicious anaemia in human beings. Naegeli,⁵ Gulland and Goodall,⁶ Davidson and Gulland,⁷ and others have drawn particular attention to the characteristic fact that persons with pernicious anaemia have an amount of vigour and capacity for work quite out of all proportion to the degree of anaemia they are suffering from. It is obvious that such persons would not seek advice till the disease was well advanced. Again, in very many cases patients suffering from pernicious anaemia present them-

* Vascular changes as distinct from oligohaemoglobinaemia and oligocythaemia, as discussed later in this connexion.

selves for examination, not for anaemia or its immediate results, but for some minor complication such as ulcers of the tongue, etc. It does not seem too much to suppose, therefore, that degrees of anaemia—short of a certain limiting but surprisingly low threshold value—may, when unaccompanied by complications which cause the patient to seek advice, have been present for long periods unobserved in the cases one is dealing with here. This is all the more likely when one considers the remissive nature of the disease and the fact that the earlier attacks are less severe than the later ones, and become gradually worse.

In his argument against anaemia being the essential cause of the disease, Collier further states that no case has been recorded or has occurred in the large series examined by himself in which the nervous manifestations developed in a patient already under observation for anaemia. Davidson and Gulland take exception to this statement in its absolute form, but, even if it is not strictly true as it stands, it nevertheless emphasizes an important phase, which has its parallel in the disease in fowls. Of the many fowls which had frank anaemia at the time the birds first came under observation, not one subsequently developed nervous symptoms, although many were kept under observation for very long periods, having regard to the age to which a fowl normally lives.

Such an occurrence, however, does not necessarily bear the interpretation which Collier puts on it. It may be that all the cases liable to be affected with nervous symptoms in the course of the disease are affected once and for all in the early stages; possibly because adaptation of the nervous system to the changed blood supply, rapid in the majority of instances, is slow in such cases. These, moreover, would constitute the cases, already referred to, where anaemia is not prominent at the time the patients come under observation. It seems likely that the enforced rest, due to the paralysis, has been effective in rendering the anaemia unobservable. Davidson and Gulland and others have stressed the great importance of rest as a therapeutic measure in bringing about remissions of anaemia and preventing relapses. It seems likely that in cases not prostrated by the initial attack there is gradual accommodation to the new conditions of the blood and its circulation, and the nervous system becomes so adjusted to the altered environment as to be immune more or less to the subsequent onset of the nervous complications.

The idea underlying the explanation suggested here is that the central nervous system can accommodate itself to a condition of anoxaemia just as it can to high barometric pressure and subsequent decompression, if in all cases the changed conditions are imposed gradually. In both sets of circumstances, however, a certain proportion of cases suffer.

Observers are not unanimous about the percentage incidence of nervous sequelae in pernicious anaemia cases. Thus Woltmann (quoted by Piney⁸) states that neurological symptoms occur in over 80 per cent. of the cases, and histological lesions of the spinal cord in a slightly greater percentage. Davidson and Gulland maintain that only 5 per cent. of the anaemic cases show definite evidence of cord damage. The nervous symptoms present in the other 75 per cent. of the cases, they state, are those that occur in any severe anaemia, and are due solely to the anaemia and cardiac weakness.

The pathological changes present in the spinal cord in this disease are minutely described by Collier. The essential lesion is a degeneration of the nerve fibres of various columns, but without any neurological proliferation to produce sclerosis and shrinkage of the cord. This characteristic absence of neuroglial proliferation must be emphasized. Piney says in this connexion that it is difficult to imagine that lesions which cause no reaction on the part of the adjacent tissues can be inflammatory in nature, and if one postulates the action of a toxin, the difficulties, he states, are perhaps even greater. Other writers have felt the same difficulty in explaining the absence of reaction on the part of the surrounding tissues. Piney attempts a solution in a manner with which I am unable to agree. He suggests that the characters of the changes give the impression that they are due to "abiotrophy" in the sense of the word as used by Gowers—

namely, the possession of a variety of hereditary constitutional weakness of the tissue.

The latest authors subscribing to the view that patients with pernicious anaemia have an hereditary constitutional weakness or diathesis are Davidson and Gulland. Their argument is that occasionally several cases of pernicious anaemia have occurred in the same family or in near relatives, which suggests the existence of a constitution predisposing to the disease. Davidson and Gulland themselves calculate that pernicious anaemia occurs to the extent of one case in twenty thousand of the general population, this being deduced from the fact that the mortality rate for the disease is 3 to 6 per 100,000 of the population. It follows that from the time pernicious anaemia was recognized and written about as a disease entity hundreds of thousands of cases must have occurred. Nevertheless, out of this total, at a generous estimate, only a few hundred individual cases have shown a familial relationship. These cases would appear to be the exceptions, and it seems likely that an explanation of their occurrence would be found along the line of similar habits, similar environment, exposure to similar producing causes, whatever these may be; or, indeed, even in terms of mere chance occurrence. A similar conclusion has been drawn from the facts that in *Bothriocephalus latus* anaemia a similar familial relationship has been discovered; that a few only of the harbourers of the parasite develop the anaemia; and also that an individual may suffer from a bothriocephalus anaemia, be cured of this by the expulsion of the parasite, and later on develop a true idiopathic pernicious anaemia.* It is difficult to see how such a conclusion could be drawn from such premisses. Disease results from the interaction of two factors: an exciting cause, and a susceptible organism on which the cause acts. Disease may appear not only in a weakened or predisposed organism—and many factors other than heredity may produce such weakness or predisposition—but in an organism subjected to more than usually virulent exciting causes. Again, as is suggested in the foot-note, the so-called idiopathic cases, which develop later, may be the direct result of the original bothriocephalus infection.

A diathesis has also been alleged to exist with regard to the appearance of disease phenomena in individual organs, such as the nervous system, the stomach, the liver, and the bone marrow (*vide* Davidson and Gulland). Allusion has already been made to Piney's statement about the part played by "abiotrophy," an inherited tendency, in the production of the nervous phenomena. Similarly, Davidson and Gulland state that the constitutional factor is found at its greatest in the central nervous system, and is generally accepted as the essential cause of the familial hereditary ataxias. But the familial hereditary ataxias are characterized by marked neuroglial proliferation and sclerosis of the cord, a condition that is characteristically lacking in pernicious anaemia. Collier, who has had an unrivalled experience of cases of subacute combined degeneration of the cord in all its forms, states categorically that heredity is not a factor in the occurrence of the disease.

Viewing the question generally, it can be said with justice that if hereditary predisposition is held responsible for lesions of the nervous system (and other systems and organs) in this disease, then it can logically be held responsible for the sequelae and complications of each and every individual disease in which complications and sequelae are irregular in their occurrence. Those cases having them would, on this basis, possess an hereditary constitutional predisposition to them of the particular organ or system affected, and *vice versa*.

In my view the nervous complications are in all likelihood the consequences of the anoxaemic condition characteristic of the disease. This conception explains the absence of the neuroglial proliferation and sclerosis of the cord; and it accounts for the site of election of the cord lesions—namely, in long tracts of the lower dorsal region, with their nutritional disabilities and difficult blood supply.

Many writers believe that achlorhydria of the stomach is an essential component of the symptom-complex of

*Evidence is accumulating that in the fowl the anaemia may persist and cause death long after the tapeworms which originated it have disappeared from the body. This would indicate that the tapeworms have set up a condition which subsequently can develop independently.

pernicious anaemia. Some even maintain that this organ has an hereditary constitutional predisposition to the disease (Davidson and Gulland). In the first place, they allege that achlorhydria is a constant in pernicious anaemia, and that in a few cases there has been evidence of achlorhydria years before the patient developed pernicious anaemia; secondly, that relatives of pernicious anaemia patients are more prone to achlorhydria than individuals in the general population, and that these same phenomena have been observed in regard to bothrioccephalus anaemia. On the other hand, however, it is indisputable that cases of pernicious anaemia occur with quite normal gastric secretions (Davidson and Gulland); that achlorhydria occurs also in ordinary secondary anaemias; that it occurs in many normal individuals and in many so-called acquired achlorhydric patients (Davidson and Gulland), about whom there is no evidence of greater liability to pernicious anaemia than in the general population.

Moreover, other explanations of the achlorhydria are more in keeping with the facts. Elsewhere⁹ I have adduced evidence to show that the condition is a sequel to the anoxaemia of the central disease. I showed that in anaemic pigs there was a considerable lowering of the alkali reserve of the blood, and that, in the cases so far examined, this was accompanied by an entire absence of acidity of the gastric contents. Having regard to the respiratory difficulties in conditions of anaemia and the importance of the "chloride shift" in respiration, these facts suggested that the achlorhydria was a direct result of the blood condition. Such a view is supported by work carried out with histamine. Thus, Katzenelbogen¹⁰ has shown that the injection of histamine causes a simultaneous rise of the alkali reserve and a secretion of acid gastric juice into the stomach, a combined result which cannot be without significance in the present issue. Bennet and Dodds's results from gastric analysis and estimation of the alveolar carbon dioxide tension point in the same direction.¹¹

Apart from these considerations, the actual anoxaemia will make it difficult for the stomach to carry out its function properly. When a remission has been produced in pernicious anaemia, say, by liver extract, the stomach has been said never again to secrete free hydrochloric acid (Davidson and Gulland). Vaughan¹² does not agree with this view, but even if it is correct it seems capable of a simple explanation along lines already indicated. The achlorhydria would at first be functional. Its persistence, however, over long periods would lead to bacterial infection of the stomach, and this, together with the anoxaemia, especially in the debilitated state of the body due to the anaemia, would result in the production of organic changes in the mucosa which would render the condition permanent. Such organic changes have, indeed, been described as present in every case by Faber and Bloch (Davidson and Gulland).

I shall now consider the part possibly played by the liver in the disease. In a prolonged discussion of the cause of megaloblastic formation in pernicious anaemia, Davidson and Gulland, after having practically dismissed the views of Pepper, Cohnheim, and Ehrlich that the megaloblastic change occurs as the result of an inborn error or constitutional defect in the marrow or of a toxin acting on the marrow (the latter on the grounds that no such toxin has ever been demonstrated), proceed to state that both these theories take a very subsidiary place to the one which they now propose to expound.* They believe that there exists in the body, principally in the liver, but also in the kidneys and to a less extent in certain other structures, a substance whose presence in sufficient concentration is essential for normal blood formation. A deficiency of this unknown but specific factor causes a megaloblastic anaemia. In spite of their recognition, by implication if not by actual statement, that this factor occurs in tissues other than those of the liver, they show nevertheless that they regard the condition as one of deficiency of the liver, and of the liver only,* in regard to this specific factor. Clearly,

on their own submissions, the kidney and other organs are equally involved.

One may, however, adduce reasons for believing that the liver is the organ mainly at fault in regard to the actual supplying of the factor. Elsewhere¹³ I have shown that in conditions of iron deficiency in pigs extirpation of practically the whole liver has a profound effect on cell multiplication in the marrow. In such conditions the marrow is intrinsically sound, but the absence of the liver factor leads to the production of normoblasts by amitotic division of the megacaryocytes. This, it should be noted, is a cell division abnormality, and indicates an influence of the liver on cell growth. In this connexion it should be emphasized that McCollum¹⁴ has shown that liver and kidney have a marked effect on cell multiplication. Further, attention may be drawn to the fact that the marrow differs from most other tissues in the body, in that cell multiplication and ripening is its main function. The others metabolize, store, and so forth; but cell multiplication in them is more or less at a standstill. These considerations may account for the practical absence of the liver factor in the marrow, where it is used up in cell multiplication; and for its presence in such quantities in, for example, the kidney, where it is not used for this purpose and can therefore be stored. There is thus considerable evidence for the view that the liver prepares a substance which has a marked influence in controlling the healthy marrow; and it seems probable that this or some allied substance may have an equally profound effect on a marrow already diseased.

Although I regard the liver as the factory where the agent is produced, I do not assume disease of the liver to be the essential primary cause of pernicious anaemia. In my view¹⁵ the liver is healthy at the beginning of the disease; but later on a vicious circle may set in and, owing to ever-increasing anoxaemia, the liver becomes more and more disabled. The marrow is, I believe, the primary seat of the disease. Under ordinary conditions one may suppose that the healthy liver produces sufficient liver agent to keep the healthy marrow under control and prevent the formation of embryonic cells. Once, however, owing to the action of some irritant, the marrow becomes disordered, the healthy liver can no longer produce enough agent to keep it in check, a vicious circle is set up, and the marrow proceeds with ever-increasing speed to complete disorganization. It is only when the agent already supplied by the patient's liver (possibly still healthy and acting to its full extent) is supplemented by an agent from outside sources that a check is put on the process.

Castle's¹⁶ work may be reviewed in the light of what has just been said. He found that when beef-steak that had been previously digested in a normal person's stomach was given in suitable amounts to a person suffering from pernicious anaemia, a typical reticulocyte response could be elicited, although the same amount of beef-steak itself, or of the digestive juices alone, or of beef-steak artificially digested in a test tube, completely failed. Castle's conclusion from these facts is that the patient's stomach lacks some factor which allows the active principle to be obtained from ordinary meat, and he believes the stomach to be the organ primarily at fault. Against such a view is the fact that in a certain number of cases of pernicious anaemia gastric digestion is normal. The phenomena can easily be explained by the supposition that, owing to the digestive disabilities of the stomach, the liver is no longer receiving the raw materials from which it can elaborate the agent or principle.

Pepper¹⁷ and Cohnheim¹⁸ held the opinion that the essence of pernicious anaemia was that the bone marrow had reverted to an embryonic type; they considered that an embryological, developmental, or hereditary factor had sufficient "drive" in itself to produce the disease. Later observers, including Ehrlich,¹⁹ extended this view by suggesting that the changes in the marrow were due to the action of a toxin. In many instances this toxin was regarded as being haemolytic. Elsewhere,¹ in connexion with this possibility, I have shown that the haemolysis, which gives rise to a haemosiderosis, is the result of the disease and not the cause of it. Moreover, haemolytic toxins produce a normoblastic or macroblastic condition of the marrow and blood, not a megaloblastic and megalocytic one.

* It is to be inferred from their argument that they regard the liver as the primary seat of the disease. Peabody (*Amer. Journ. Path.*, 1927, iii, p. 179) and others had already emphasized the importance of the liver.

There would seem to be little doubt that a toxin or an allied substance acting on the marrow is at the root of the production of the disease. Here, by its irritative or stimulating action, it produces a specific type of marrow change. There is no evidence for the view that the lesions in the various organs in pernicious anaemia are produced directly by the same toxin or by a variety of different toxins. Everything suggests that the conditions in the nervous system, stomach, and liver (in the later stages) are produced secondarily by the anoxaemic state brought about by the primary marrow lesion. Any other view would seem to be incapable of explaining how such diverse causes as those producing idiopathic pernicious anaemia, sprue, and the pernicious anaemia of pregnancy, syphilis, tapeworm infestation, malaria, etc., can so uniformly bring about what Vaughan calls these "oddly associated lesions."

Summary.

The essential and primary factor in the production of pernicious anaemia is the involvement of the bone marrow in an irritative process, which causes it to revert to embryonic cell formation.

The resulting anoxaemia causes, secondarily, the complications which are to be found in the central nervous system, the stomach, and the liver (later stages).

There is no evidence for the existence of a "pernicious anaemia diathesis" either in relation to the disease as a whole or to the organ complications.

I wish to express my indebtedness to Mr. Archibald Macdonald, M.A., B.Sc., for supplying the fowls; to Dr. Marion B. Richards and Mr. Kenneth McKenzie, M.Sc., for preparing the photographs; and to the Carnegie Trust for the Universities of Scotland for a grant towards their reproduction.

REFERENCES.

- McGowan: *Pernicious Anaemia, Leukaemia, and Aplastic Anaemia*, 1926.
- McGowan: *Edin. Med. Journ.*, 1930, 37, p. 85.
- Collier: *Price's Textbook of Practice of Medicine*, 1922.
- Osler and McCrae: *System of Medicine*, vol. vii, p. 130.
- Naegeli: *Blutkrankheiten und Blutdiagnostik*, 1923, p. 366.
- Gulland and Goodall: *The Blood*, 1925.
- Davidson and Gulland: *Pernicious Anaemia*, 1930.
- Piney: *Recent Advances in Haematology*, second edition, 1928.
- McGowan: *Edin. Med. Journ.*, 1930, 37, p. 28.
- Katzenelbogen: *Journ. Amer. Med. Assoc.*, 1929, 22, p. 1240.
- Bennet and Dodds: *Brit. Journ. Exp. Path.*, 1922, 2, p. 58.
- Vaughan: *Quart. Journ. Med.*, 1930, 90, p. 217.
- McGowan: *Proc. Roy. Soc. Med.*, 1928, 21 (Sect. Comp. Med., p. 33).
- McCollum: *The Newer Knowledge of Nutrition*, 1923.
- McGowan: *Edin. Med. Journ.*, 1930, 37, p. 350.
- Castle: *Amer. Journ. Med. Sci.*, 1929, 178, p. 748.
- Pepper: *Ibid.*, 1875, 70, p. 313.
- Cohnheim: *Virchow's Archiv*, 1876, 68, p. 291.
- Ehrlich and Lazarus: *Histology of the Blood*, Meyer's translation, 1900.

THORACIC STOMACHS:

A STUDY OF PHARYNGEAL POUCH AND CARDIOSPASM, WITH REPORT OF THREE CASES.

BY

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(With Special Plate.)

For several decades occasional observers have reported cases of simple dilatations of the oesophagus resembling adventitious stomachs, but they are only now becoming readily recognized. For this recent facility in diagnosis we have to thank Roentgen. Radiography, after the ingestion of an opaque meal, makes the diagnosis of such

FIG. A.—Showing upper and lower thoracic stomachs in profile in the chest.

intrathoracic enlargements one of easy and convincing clarity instead of recondite conjecture, as when the doctor depends wholly on clinical acumen.

These expansions are found at the upper and lower ends of the gullet. In shape and in their relationship to the parent gullet they resemble aneurysms, such as occur in the adjacent aorta. The upper is saccular and the lower fusiform in outline. A diagram of them in profile indicates their deep dwellings in the chest—and the reason for the picturesque title of these remarks (Fig. A). As a matter of fact, the title is not an abuse of the word "stomach," but a reversion to its proper use, for "stomach" is derived from the Greek word meaning "gullet," and Galen, among other anatomists, preferred the name "ventricle" for the subdiaphragmatic stomach. They are familiar as "pharyngeal pouch" or "diver-

ticulum," the lower one occurring in the condition known as cardiospasm. Diaphragmatic hernia of the normal stomach into the thorax is not included in this paper.

It is hoped that reasons other than the mere infrequency and pathological curiosity of these conditions will make this communication helpful. A doctor's duty to his patients makes it necessary to recall these disorders to mind from time to time. Their remoteness in the hidden depths of the chest hides them from simple view, and the old saying still holds good—"Out of sight, out of mind." While failure to recognize some lesions makes little practical difference to the patient, this is not true in the case of thoracic stomachs. They disable the victim, progressively and gravely, if left to nature, but, despite their inaccessibility, they are amenable to sure relief by surgery. Reports on such cases, rare but vital, keep the doctor on the look out for them.

A few notes of illustrative cases will serve as a basis for consideration of the clinical features of these alimentary pouches.

CASE I.

W. H. C., aged 62, was a monumental mason, but had only been a supervisor for the last fifteen years. He came to me in August, 1929. His past health had been good. He stated that for ten years queer audible noises occurred during swallowing. Three years ago vomiting—as from a pump—started and brought relief. For nine months there had been increasing dysphagia and vomiting. This was lately so severe that life had become unbearable; he was rapidly losing weight, and had increasing constipation for five months. He sought urgent relief in order to nourish himself. He had been disposed to heart attacks, having fainted three times in the street, and he had swelling of the feet.

On examination he was somewhat pale and spare in flesh. His teeth were offensive. There was no swelling in his neck, but there was a feeling of food stoppage behind the upper ribs. A vomit of six ounces by his bed looked like creamy tomato soup. It was acid to litmus, due to decomposition, not, presumably, to admixture with gastric juices, and inoffensive in odour. Vomiting occurred within, at the most, a few minutes of ingestion. Pharyngoscopy by Mr. Angell James revealed the walls of the pouch, but no exit.

He was radiographed after the ingestion of an opaque meal, when the barium was seen to occupy a substernal pouch the shape of half a small orange, with the flat surface upwards (Figs. 1 and 2). It was median, with a slight bulge to the right, and its smooth, convex lower aspect was at the level of the fourth dorsal vertebra.

Similar cases reported in the literature occur mostly in patients of the fifth decade, and are of several years' duration. Sensations of strangling and of troublesome coughing on recumbency are noted, as well as regurgitation of food on pressure of the left side of the neck. The patient referred to above showed diminished nutrition, for thoracic stomachs, unlike their abdominal congener, boast no digestive attributes, but rather impede the process.

FIG. 2.

FIG. 1.

FIG. 3.

FIG. 5.

FIG. 4.

FIG. 1.—Hen 107, Case III. Lumbar enlargement of cord, Marchi's method; showing marked degeneration in the dorsal columns, also some in the anterior and antero-lateral.
FIG. 2.—Hen 360, Case VII. Lower dorsal region of cord, Marchi's method; showing marked degeneration in the dorsal, anterior, and antero-lateral columns.
FIG. 3.—Hen 105, Case II. Section of spleen, potassium ferrocyanide and HCl; showing marked haemosiderosis in the splenic pulp.
FIG. 4.—Hen 121, Case IV. Section of liver, potassium ferrocyanide and HCl; showing marked haemosiderosis of the Kupffer cells and also diffuse haemosiderosis in the liver cells.
FIG. 5.—Hen 223, Case VI. Section of kidney, potassium ferrocyanide and HCl; high power, showing marked haemosiderosis of the secreting convoluted tubules.

FIG. 1.—(a) Skiagraph of Ptolemaic femur; (b) photograph of same; (c) skiagraph of humerus in hospital patient, for comparison.

FIG. 2.—(a) Photograph of pre-dynastic jaw; (b) skiagraph of same.