PERNICIOUS ANEMIA CAUSED BY DIPHYLLOBOTHRIUM LATUM, IN THE LIGHT OF RECENT INVESTIGATIONS

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The macrocytic anemia caused by the broad fish tapeworm, Diphyllobothrium latum, has been the subject of extensive investigations in Finland, starting with the pioneer work of J. W. Runeberg (1887) and O. Schauman (1894).

The fish tapeworm is extraordinarily common in the country. In certain provinces more than 90 per cent of the population is infested with the parasite. Of the total population of the country, which is about 4,000,000, one half to one million can be considered to be tapeworm carriers. The parasite is found in persons of all ages, even in children under 1 year of age.

For most of these carriers, the worm is a relatively innocent parasite, but in some, it causes a macrocytic anemia. According to earlier investigations (R. Ehrstrom, 1926) the frequency of anemia was estimated to be 1 case in 5,000-10,000 worm carriers. But, if the blood of worm carriers is examined systematically, a far greater number of anemia cases can be shown. Among the conscripts of 20 years of age admitted to a military hospital in peace time, Seppa (1927) found 1 case of anemia in 659 worm carriers. G. Tötterman (1944), in a community strongly infested with tapeworm, noted, in 1942, 1 case of anemia in 136 carriers; and in 1943, he found the frequency to be 1 case of anemia in 383 carriers. In a war hospital, from 1941 to 1944, I found 96 instances of tapeworm anemia in about 11,000 medical cases. The number of worm carriers in this group, composed of men from 18 to 40 years of age, is not known.

The above figures give a good idea of the importance of the problem of tapeworm anemia in Finland. This anemia is a typical "pernicious anemia" with a characteristic blood picture and a megaloblastic bone marrow, agreeing in all respects with that found in "cryptogenetic" Addisonian anemia. A pernicious tapeworm anemia can also be brought to remission with liver preparations per os or parenterally, or with stomach preparations per os without removal of the worm.

In contrast to cryptogenetic pernicious anemia, tapeworm anemia occurs even in people under 20 years of age. In most cases there is an achlorhydria after the injection of histamine; though, especially in younger patients, the gastric juice often contains free hydrochloric acid and is secreted in the usual quantities. Signs of spinal cord involvement are less apparent than in cryptogenetic pernicious anemia.

That the illness is really due to the worm infestation is proved by the fact that complete remission takes place after the worm is expelled without any further need for antianemic treatment.

Since cryptogenetic pernicious anemia is not rare in Finland and worm infestation is common, it is natural that now and then both types of anemia should occur simultaneously in an individual. In such cases, of course, there is no remission after the worm cure. In fact, the anemia often becomes more severe.

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G. Tötterman (1944) says that he has encountered cases of mild macrocytic anemia in tapeworm carriers that did not respond to liver treatment but showed good remission after a worm cure. He assumes that the pathogenetic mechanism for this form of anemia is different from that for the true pernicious tapeworm anemia, which does respond to liver therapy.

On the other hand, there have been numerous reports in Finland of cases of hypochromic anemia in tapeworm carriers which were not cured by expelling the worm. On this point, conflicting information is still found in the literature.

The question which is of special interest for research is: why do so few worm carriers have pernicious anemia? Or formulated in greater detail: what are the factors which lead to the rise of worm anemia and why are these factors active in only a small number of cases?

Hitherto, these questions have not been satisfactorily answered. The discussion of them and the tapeworm anemia problem as a whole has been reported in detail by Birkeland (1932).

The present knowledge of the genesis of pernicious anemia suggests that in some way the worm interfered with the production or absorption of the antianemic factor or with the production of the components involved in its formation. This thought was first expressed by Saltzman (1935). On the basis of similar reasoning the pernicious anemia in connection with sprue, ventricular lesions, intestinal resections, etc., can, as is well known, be explained.

An investigation is here reported carried out on these lines with the object of explaining the pathogenesis of cases of pernicious anemia, most of them due to tapeworm infestation. The tests have been going on since 1937.

1. The Intrinsic Factor

   a) The course of remission after removal of the worm. If the worm is expelled in the usual way (with 3–4.5 Gm. Extraction filicis) from hospital patients on an unrestricted diet, a blood remission begins shortly afterwards and continues until the blood picture has become normal. In a group of 7 cases, it was observed that the reticulocytosis began on the fourth to the sixth day after the worm was expelled in 6 of the patients and in 1 case, not until the eleventh day. The reticulocyte maximum was reached in the first 6 cases mentioned between the seventh and the tenth day after the worm cure, and in the seventh case on the thirteenth day. The maximum reticulocyte values varied between 7.4 and 23 per cent. In these cases, examination of the blood before Extractum filicis was given showed that the erythrocytes were between 1.2 and 2.1 million per cu. mm. of blood.

   Apparently, after the worm cure, the reticulocytosis generally sets in a few days later than after a strong initial liver treatment. The maximum for reticulocyte values is on the average somewhat lower than in cases of pernicious anemia treated with liver, but on the other hand, the reticulocyte crisis lasts longer. The increase of the erythrocytes is generally about 100,000 per day, which is just as great as with adequate liver therapy.

   It has been found by means of a sternal puncture that within 48 hours after the
worm cure, the megaloblastosis in the bone marrow gives way to a normoblastic type of regeneration.

The most rational therapy in pernicious tapeworm anemia is the simple worm cure. Only in very severe anemia is it necessary to start treatment with liver injections and not expel the worm until after the blood picture has improved. In such cases, however, it is difficult to decide afterwards whether the pernicious anemia was caused by the worm or not. Only if the patient is very young and/or has free hydrochloric acid in the gastric contents can one be to some extent certain that the pernicious anemia was caused by the tapeworm.

The fact that the pernicious tapeworm anemia is completely cured after the worm is expelled can be explained in no other way than that the patients have access to all the substances required for the endogenous formation of the antianemic principle. Evidently, these substances are available directly after elimination of the worm, as indicated by the promptness with which the remission begins thereafter. If the food contains the extrinsic factor, this must imply above all that the intrinsic factor becomes at once available.

b) Castle’s test with gastric juice from patients with pernicious tapeworm anemia. Hernberg (1936–1941) has shown that the gastric juice in patients with pernicious tapeworm anemia, as well as in persons who have had it, contains intrinsic factor. Mixed with meat, such gastric juices produce a typical remission when given to patients with cryptogenetic pernicious anemia.

c) In vitro experiments. The author has made some investigations of the proteolytic gastric enzyme active at neutral reaction according to the method given by Taylor et al. (1938), and has found (1940) that this enzyme occurs in pernicious tapeworm anemia as well as in cryptogenetic pernicious anemia, though in the latter cases the total amount of the gastric secretion is very much reduced. It has been suggested that this enzyme is identical with the intrinsic factor. My results have been confirmed by Helander (1945). Hernberg (1939) with Lasch’s reaction has obtained similar results in the gastric juice from patients with pernicious tapeworm anemia.

The investigations here reported, all support the idea that the gastric juice of patients with pernicious tapeworm anemia contains intrinsic factor. In spite of this, and in spite of the fact that the amount of gastric juice is often normal, an anemia has arisen. Apparently the pernicious anemia in tapeworm carriers is not caused by cessation of the secretion of the intrinsic factor because of the presence of the worm. However, it is evident that some inhibition of the gastric juice secretion may occur in connection with pernicious tapeworm anemia, for in some cases free hydrochloric acid reappears in the gastric contents after the remission in patients who showed achlorhydria while the anemia was apparent.

The author has been unable to find any difference in the speed of remission after a worm cure in patients with achlorhydria and those with normal gastric secretion.

It seems possible that a decreased secretion of intrinsic factor may facilitate the occurrence of a pernicious anemia in connection with tapeworm infestation. It is well known that some people who have had a pernicious tapeworm anemia when young, have later fallen ill with a cryptogenetic form of the disease. In some
families many cases occur of both cryptogenetic anemia and pernicious anemia due to worm. The cause of this has been considered a special "constitutional disposition" for this type of anemia. It may be that this "disposition" consists in a deficient production of intrinsic factor.

2. The Extrinsic Factor

a) Clinical observations. Experience in Finland shows that worm carriers can have pernicious anemia even though their food contains a sufficient amount of protein of different kinds. Apparently, lack of extrinsic factor is not essential for the occurrence of pernicious tapeworm anemia (in contrast to some other conditions such as, for example, the nutritional tropical pernicious anemia). However, certain facts do support the idea that a relative deficiency in extrinsic factor can contribute to the rise of the disease. G. Tötterman found in his material a higher frequency of pernicious tapeworm anemia in 1942 than in 1943. In the former year the food situation in our country was particularly serious; there was a special lack of proteins. The next year the situation had improved considerably. My own experience agrees with that of Tötterman's. In some cases of worm anemia, I have seen a slight reticulocytosis and even a certain improvement of the erythrocyte count during the administration of meat. This was the case with soldiers who came for treatment directly from the front. Cramer (1911) observed pernicious tapeworm anemia at the same time in 3 sisters who, by reason of some mental peculiarity, lived like hermits and fed themselves with an extremely insufficient diet.

b) The course of remission after removal of the worm in the absence of extrinsic factor. It is logical to assume that there will be no remission after the worm is expelled if the patient, shortly before and after the worm cure, has taken food containing no extrinsic factor. The correctness of this reasoning has been shown in a series of twelve tests. When the patients were admitted to the hospital they were placed on a basic diet as free from extrinsic factor as possible. After some days, they were given a worm cure. Very insignificant signs of blood regeneration, or none at all, were observed even after twelve to fifteen days. On the contrary, the blood picture often became progressively more abnormal. As soon as substances known or believed to contain extrinsic factor were added to the diet, a marked reticulocytosis began and the blood picture improved rapidly. It has been proved that this is true when meat, milk, Hammarsten's casein, pepton, brewer's yeast and concentrated yeast extract and, to a lesser degree, soy bean protein were added to the diet. These observations confirm Castle's theory that both intrinsic and extrinsic factor are necessary.

The method furnishes a means of testing substances for their content of extrinsic factor.

One practical conclusion is that, after worm cure, patients with worm anemia must be given a diet rich in proteins if a rapid remission is to be expected.

3. The Interaction between the Intrinsic and Extrinsic Factors

Castle's test has not been previously carried out on patients with pernicious tapeworm anemia, yet this experiment is of great importance. It is conceivable that
the worm in the intestinal canal prevents the interaction between extrinsic and intrinsic factors and in this way gives rise to the pernicious anemia. If this is true, it would be expected that no remission would occur when a patient is given a mixture of meat and gastric juice. This would indicate that the worm has been able to destroy the effect of these substances supplied from outside in the same way as it prevents the body's own intrinsic factor from interacting with extrinsic factor in the patient's ordinary food. If a fresh mixture of gastric juice and meat proves to be ineffective while the same mixture incubated for six hours at 37°C. does have an antianemic effect, the conclusion might be drawn that by means of the enzyme activity in vitro, some new substance is formed which the worm is unable to injure.

A series of 14 tests was carried out to clear up this question. Meat (150 Gm. per day), or in some tests yeast extract, was used as the source of the extrinsic factor. The daily amount of gastric juice with which the meat or yeast was mixed was 150-175 ml. Each test period lasted eight days. During the first test period a nonincubated mixture was given.

In some cases of cryptogenetic pernicious anemia these tests produced a splendid remission. The effect was equally good whether the mixture was incubated previously or not. On the other hand, the test results were clearly negative in cases of pernicious tapeworm anemia. Neither fresh nor incubated mixtures of meat and gastric juice produced any remission. In some cases the identical gastric juice was used as in parallel tests with cryptogenetic pernicious anemia. The remission occurred only after the worm had been expelled.

In one case of pernicious tapeworm anemia, 100 ml. of gastric juice was brought up daily after insulin stimulation, and was incubated with 150 Gm. of meat for six hours, after which the mixture was administered to the patient. Not even in this way could any remission be produced.

These observations give strong support to the idea that the worm in the intestinal canal is capable of preventing interaction between the extrinsic and intrinsic factors and that such an inhibition can be deemed to be the reason for the pernicious anemia.

The fact that incubation does not involve an improvement of the antianemia effect of meat and gastric juice confirms the assumption that the antianemic principle cannot be formed in vitro but only in vivo. It is possible that the interaction between extrinsic and intrinsic factors takes place in the intestinal wall (Formijnen, 1940). Perhaps this interaction is not a simple enzyme reaction.

4. The Liver Factor

If the worm in pernicious tapeworm anemia is expelled and the formation of new antianemic factor is prevented by giving a diet free from extrinsic factor, then, as already stated, there is no blood remission. This shows that the liver must be deprived of its stock of antianemic factor, for if any were present, blood regeneration should take place after the anemia-producing worm had been removed, independently of the supply of intrinsic and extrinsic factors.

It is conceivable that the worm may destroy the antianemic factor at the place where it is assumed to be formed, i.e. in the intestine. Another possibility is that
the worm toxins absorbed from the intestine may destroy the entire quantity of antianemic liver factor available in the body, but this is an improbable theory.

It is a priori somewhat improbable that the tapeworm can injure the liver factor, partly because it is rather stable and partly because we know that the administration of liver preparations both parenterally and per os quickly cures a pernicious tapeworm anemia.

I have incubated ordinary injectable liver extracts together with worm in vitro at 37° C. for some days and could not, at least in this way, prove any decrease of their antianemic effect.

It appears, then, that the lack of the liver factor is not the result of destruction by the tapeworm itself nor by toxins from the worm.

5. Folic Acid

I have treated 4 cases of pernicious tapeworm anemia with folic acid per os. An excellent remission was obtained in all cases with doses of 20-30 mg. daily for 7-10 days, showing that folic acid also is not injured by the worm.

6. The Absorption

The clinical picture in pernicious tapeworm anemia gives no reason to believe that the absorption in this disease is impaired. Carriers of Diphyllobothrium latum seldom suffer from severe intestinal disturbances. Worm carriers with and without anemia do not differ from each other in this respect. In no case are the conditions comparable with those in sprue, intestinal anastomoses, etc.

The glucose tolerance test has been carried out in 4 cases of pernicious tapeworm anemia, both before the worm cure and after the blood had become normal. In all cases the blood sugar curve had a normal course both before and after the worm cure; thus it was not possible to show that there was any disturbance in the glucose absorption.

7. Experimental Feeding with Tapeworm Preparation

The effect on the blood of giving worm preparations per os or parenterally has, of course, been studied in both animals and humans. T. W. Tallqvist (1907) experimented on himself in this way and G. Tötterman (1938-1940) has published a large series of tests. Both have thought they saw a certain anemising effect from the preparations they used. I am not convinced of the correctness of their conclusions for reasons stated in another publication.

The problem has been attacked by attempting to answer the following questions: (1) Is the antianemic effect of the mixture of gastric juice and meat nullified if worm is added? (2) Is the remission after the worm cure absent in worm anemia patients if the worm preparation is given per os?

The mixtures of gastric juice and meat (or yeast extract) were prepared in the same way as described earlier. The subjects were patients with untreated crypto-genetic pernicious anemia. First they were treated for eight days with gastric juice plus meat (or yeast extract) with the addition of a considerable amount of fresh or dried Diphyllobothrium latum. The remission was always splendid. During the
following period with gastric juice plus meat (or yeast extract) without the addition of worm, no new reticulocytosis was observed and the blood regeneration was no more rapid than during the first test period.

In one case of worm anemia the patient, after the worm cure, was given worm powder per os in increasing amounts. In spite of this the blood improved in the usual way.

In some tests the worm anemia patients were kept on a diet free from extrinsic factor, were given worm cure and then for eight days extrinsic factor in the form of yeast extract with the addition of worm powder. In spite of this addition the blood improved rapidly.

In connection with these tests, worm powder was mixed with hog’s stomach in order to investigate the possibility of loss of antianemic effect. In spite of the addition of powdered worms in two such tests the hog’s stomach still had a marked antianemic effect.

It was thus shown that addition of worm is unable to destroy the antianemic effect of mixtures of gastric juice and extrinsic factor, or of stomach preparations. Moreover, the presence of worm does not prevent the remission after the elimination of the worm in worm anemia. This fact has been interpreted to mean that the inhibition of the interaction between the intrinsic and extrinsic factors can be produced only by the living worm in its natural surroundings at the place where the interaction occurs.

8. Inhibition in Vitro of the Proteolytic Activity of Gastric Juice at Neutral Reaction

The gastric protease which is active at a pH range from 5 to 9 is greatly inhibited in its hydrolytic capacity in vitro after the addition of even relatively small amounts of Diphyllobothrium latum. The inhibitory substance is destroyed by heating to 80°C for twenty minutes. It is not dialyzable and is not soluble in ether, nor in 98 per cent ethyl alcohol. It cannot be precipitated with 50 per cent alcohol, but can be precipitated quantitatively in 90 per cent alcohol.

The gastric protease in question has been assumed to be identical with the intrinsic factor, and the hydrolysis of casein in vitro has been considered as corresponding to the interaction between the intrinsic and extrinsic factors in vivo. It has not yet been possible to prove this assumption. As stated above it seems probable that such interaction cannot occur in vitro but only in the intestinal canal.

There is thus a discrepancy as follows: (a) The living worm in situ seems to inhibit the interaction between the extrinsic and intrinsic factors, (b) the administration per os of worm preparations does not inhibit this interaction, while again (c) the addition of worm in vitro inhibits the proteolytic activity of gastric juice at neutral reaction. It seems that this discrepancy cannot be explained until we have more detailed knowledge of the different substances here concerned. The exact chemical nature of the extrinsic factor, intrinsic factor and the tapeworm toxin are as yet unknown.
9. The Localization of the Tapeworm in the Intestinal Canal

Presumably the worm cannot inhibit the reaction between extrinsic and intrinsic factor unless the worm is present at the place where the interaction occurs. Now the question arises: Where in the intestinal canal is the worm to be found? Very uncertain information on this point is available. Experience from operations and autopsy in general indicate that the worm has been chiefly observed in the ileum, but there are no systematic observations of this fact. Sometimes it happens that Diphyllobothrium latum is vomited, which shows that at least occasionally it can be very high up in the intestine. To investigate this question, the author made a series of intestinal intubations. As the Diphyllobothrium latum produces large quantities of eggs it was relatively easy to determine at what distance from the mouth the first eggs could be aspirated. In many cases small pieces of the worm itself were aspirated at the same time. Of course, it is not possible to calculate in this way the highest point in the intestine where the worm is attached. Although no eggs are produced from the highest segments of the worm, yet I have been convinced that results can be obtained which allow comparison between different cases.

The intubations were carried out on 26 worm carriers who were divided into 4 groups as appears in table 1, in which the results are also summarized.

The results show that in manifest pernicious anemia the worm is found higher up in the intestine than otherwise. Perhaps one can imagine that in that region it is better able to interfere with the interaction between extrinsic and intrinsic factors. How high up in the intestine the worm must be for it to inhibit this reaction is difficult to determine. My results favor the opinion that a "critical limit" lies 140-150 cm. from the mouth, which ought to be about the borderline between the jejunum and the ileum.

10. An Attempt to Explain the Pathogenesis of the Pernicious Tapeworm Anemia

As described above, it appears to be possible that the Diphyllobothrium latum causes pernicious anemia by inhibiting the interaction between extrinsic and intrin-
sic factors, but that this reaction can occur only if the worm is sufficiently high in the intestine. However, as stated previously, there is reason to presume that the amount of extrinsic factor in the food and of intrinsic factor in the gastrointestinal canal is also of some importance. Thus whether anemia occurs or not would depend on a definite correlation among these three determinants: the amount of extrinsic factor, the amount of intrinsic factor, and the worm's high or low position in the intestine.

Finally a time factor must also be taken into consideration. The formation of antianemic factor must have been inhibited for such a long time that the liver is wholly deprived of it. Only then is there reason to expect that the anemia will manifest itself.

It must be emphasized that in the great majority of cases of pernicious tapeworm anemia, there is no basis for the assumption that either a defective diet or a hereditary disposition are to be reckoned with as co-operating causes. Most tapeworm anemia patients do not fall ill later with a cryptogenetic anemia. I can, therefore, not confirm the correctness of Birkeland's conclusion that 'it seems appropriate to classify surviving patients with Diphyllolothrium anemia as suffering from abortive forms of genuine pernicious anemia.' My view of the problem is that in principle any worm carrier whosoever can get a pernicious tapeworm anemia if only the worm—ceteris paribus—is high enough up in the intestine. If the worm is expelled a complete restitution can follow.

The theory I have formulated explains—in my opinion—the following circumstances which have been specially put forward by Saltzman (1924) and which have hitherto been difficult to interpret.

a) A person can carry Diphyllolothrium latum for many years before he falls ill with pernicious anemia. The explanation of this can be that the worm, for one reason or another, has invaded the upper parts of the intestine, sometimes possibly as a reinfection.

b) A person who has had pernicious worm anemia and becomes well after the worm is expelled does not necessarily get anemia if he is again infested with worm. At the reinfection it may happen that the worm is only in the lowest parts of the intestine.

c) A worm expelled from an anemia patient is often disintegrating and discolored. Sometimes no worm at all is seen in the feces. According to my theory, this disintegration can be due to the fact that the worm, being higher up in the intestine has had a longer distance to go before it was expelled. During its passage through the intestine it has had to undergo a strong autolytic decomposition and is also affected more by the digestive enzymes than if it had been in the lower part of the small intestine and only had to pass through the colon, where the enzymes are less active.

d) The amount of worm is not in correlation with the occurrence of anemia. A small amount of worm can cause anemia if it is sufficiently high up in the intestine, while a large amount does not necessarily do so if it is collected in the lower part of the small intestine. Yet cases with very large amounts of worm, 80-100 M. and more, are often accompanied by anemia. In such cases it can be imagined that the worm, because of its great volume, has been forced upwards towards the jejunum.

e) Spontaneous remission with a return to normal blood values are not rare in worm
anemia. The explanation of this can be that the worm had deserted the upper parts of the small intestine and wandered down towards the ileum. In my 3 cases of this type the worm was found just as low in the intestine as in nonanemic worm carriers (cf. table 1).

f) Remission after an incomplete worm cure can also occur. A filicin cure can fail in such a way that only a small amount of the worm, or none at all is expelled, and after the cure worm eggs can still be seen in the feces. In spite of this, the blood improves. At a later worm cure—after the blood picture has become normal—a considerable amount of worm is often removed. In such cases—according to my idea—the worm at the first "unsuccessful" cure was driven from the upper part of the intestine but remained in the lower part where it was no longer able to exercise its anemia-producing effect.

This idea was confirmed by the following test. In one case of manifest pernicious worm anemia the eggs were found 115 cm. from the mouth. Through the intestinal tube 2 Gm. filicin emulsion were instilled. The worm was not expelled and the feces continued to contain worm egg, but they could not be demonstrated as present at the former depth (115 cm.). A few days after the filicin cure a marked reticulocytosis began and the blood picture improved rapidly. The tube was then allowed to glide farther in, and worm eggs were not found till 200 cm. from the mouth, that is, far down in the ileum. Following another treatment with filicin, 31 M. of ordinary looking Diphyllobothrium latum were expelled.

**Comment**

According to one earlier theory, the occurrence of worm anemia may be due to a change in the character of the parasite, possibly an abnormal disintegration of the worm in the intestine, but I have been unable to find any signs of such a disintegration. The worm segments which I sometimes aspirated at intubation from worm anemia patients have been very motile and of ordinary appearance. According to other theories, the cause of the anemia lay in the host. These theories have presumed a varying permeability of the intestinal wall to the worm toxin, a special, individual susceptibility of the hemopoietic organs to it, or an allergic preparedness; G. Tötterman has classed the pernicious tapeworm anemia with the malignant granulocytopenia due to the use of amidopyrine. Apart from the fact that I find the experimental basis of these theories defective, none of them seem to me to explain the worm anemia problem satisfactorily. It appears artificial to conceive of the macrocytic anemia with its megaloblastosis as an allergic reaction. Another fact that tells against the toxic and allergo-toxic theories is that the anemia can be cured with liver or stomach preparations without expulsion of the worm. Again, on the basis of them, it is difficult to explain why no remission occurs after the worm cure unless extrinsic factor is available. The circumstances listed under Section 10 (a-f) above are also not easy to explain.

There is no doubt that Diphyllobothrium latum contains a powerful poison. If one handles fresh worm with unprotected hands, the skin is greatly irritated. If one places a small amount of dried and pulverized worm on the tongue, there is a feeling of burning. The inhalation of worm powder has been proved to produce nausea,
fever, rhinitis, asthmatic cough and eosinophilia in the blood. A worm carrier often suffers from giddiness, various nervous manifestations and nausea, has eosinophilia (which may or may not be absent in anemia cases) and shows serological changes. Like the macrocytic, nonpernicious anemia described by G. Tötterman, these phenomena can be considered as the expression of the effects of toxic activity, resembling those which condition the rise of pernicious anemia. Thus, according to my idea, the inhibition of the interaction between extrinsic and intrinsic factors is only one expression of the worm's toxicity.

Tests on animals with worm preparation injections also bear witness to the toxicity of the worm. Among other things, it appears to contain a hemolytic toxin. Yet it has not been possible with these tests to produce an anemia which directly corresponds to the Addisonian anemia in man.

Much confusion in the discussions could, I believe, be avoided if the ability of the worm to produce pernicious anemia was consistently kept separate from its other toxic properties.

Certain details in the tapeworm anemia problem still await solution. Like the cryptogenetic pernicious anemia, the pernicious tapeworm anemia shows definite variations in its seasonal distribution. It is most usual during the period from March to August. Illustrative curves with which my own experience agrees are to be found in Birkeland's monograph. It is at present impossible to decide to what extent these seasonal variations depend on circumstances in the patient himself: on light conditions, on the contents in the diet of protein, folic acid (as suggested by Waldenström), or other substances. A racial factor (in connection with pigment metabolism) must also be taken into consideration in both forms of pernicious anemia.

The chemical nature of the worm's toxin is still unknown. If that could be determined, it might be possible to get a better idea of the process by which the poison interferes with the interaction between the extrinsic and the intrinsic factors.

I have tried to show here that the investigation of pernicious worm anemia has not only a local interest but can also contribute to the elucidation of the whole great question of the macrocytic and megaloblastic anemias which respond to liver treatment and which are termed "pernicious."

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