An Address

ON

ADDISON'S (PERNICIOUS) ANAEMIA AND
SUBACUTE COMBINED DEGENERATION
OF THE SPINAL CORD.*

BY

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NOMENCLATURE.

In a paper read before the South London Medical Society in 1849, Thomas Addison,¹ physician to Guy's Hospital, referred incidentally to a "remarkable form of anaemia," and six years later his classical description of the disease appeared in his monograph, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*.

In 1871 Biermer² of Zürich published a paper on progressive pernicious anaemia, in which, however, he added nothing to our knowledge of the disease described by Addison twenty-one years earlier beyond pointing out the frequency of retinal haemorrhage. On the other hand, he added much confusion by including under a single name both Addison's "idiopathic anaemia" and a great variety of other conditions associated with anaemia. The designation "Biermer's anaemia," which is employed in Germany and Switzerland, is therefore quite unjustified. The name "pernicious anaemia," having been introduced by Biermer for an entirely different purpose, is equally unsuitable, as well as being most undesirable on account of the depressing significance it has for the sufferer. As the investigations of the last twenty years have shown that the disease is almost certainly due to infection of the intestinal tract, the original name of idiopathic is no longer correct. Addison's description of the disease is so admirable that I am convinced that no more suitable name could be devised than Addison's anaemia, as William Hunter³ first suggested in 1909.

FIG. 2.—Curve of red corpuscle diameters in case of Addison's anaemia, compared with normal. (J. W. Shackle and A. C. Hampson.)

THE BLOOD IN ADDISON'S ANAEMIA.

The most characteristic features of the blood in Addison's anaemia are now recognized as being the great inequality in the size of the red corpuscles—the anisocytosis—due to the presence of microcytes and megalocytes, and the increase in their average size in spite of the presence of some cells far smaller than the smallest cells found in normal blood. This feature is present in the very earliest stages and almost

always during remissions, even when there is little or no actual anaemia present.

Price-Jones⁴ has introduced an extremely valuable graphic method of recording the size of the blood corpuscles. Five hundred cells are accurately measured and the number of each size is charted, the size being shown horizontally and the number vertically. The middle curve in Fig. 1 represents that obtained from the measurement of 10,000 cells of twenty normal individuals reduced for comparison to the size of a curve of 500 cells. It will be seen that the total variation in size of the corpuscles is not great. The sizes of 10,000 cells measured by Price-Jones in twenty cases of Addison's anaemia, and those of 5,000 cells in ten cases of anaemia secondary to haemorrhage, are shown in the same figure. In Addison's anaemia the whole curve moves to the right and has a very wide base, owing to the presence of very small microcytes and very large macrocytes. Fig. 2 is a chart made for me by Mr. J. W. Shackle and Mr. A. C.

FIG. 1.—Curves of red corpuscle diameters in healthy persons, haemorrhagic anaemia, and Addison's anaemia. M = mean diameter of red corpuscles. (Price-Jones.)

Hampson of a case of Addison's anaemia superimposed on Price-Jones's normal curve. It shows the characteristics I have mentioned, and in addition the irregular form always seen with Addison's anaemia, which is in striking contrast with the uniform curve obtained with normal blood, and with the curve in secondary anaemia, in which the highest point moves to the left, the curve is comparatively uniform, and the total variation in size of cells is not much greater than normal. Charts of this kind are very laborious to make, but they are of the greatest value in diagnosis in doubtful cases, as the characteristic curve is present in Addison's anaemia before the patient is actually anaemic and also during remissions, and they give a useful

graphic record of the progress of each given case (Fig. 3).

Nucleated red corpuscles, and especially megaloblasts, which have generally been regarded as of great importance in diagnosis, are much less characteristic of the disease. They are never present throughout the illness, and very rarely either in the early stages, when diagnosis is most important, or during remissions. A prolonged search is often required to find a single megaloblast, and in some cases they are not discovered at all. The same is true of polychromasia and punctate basophilia. The presence of these abnormal types of corpuscle is evidence of an unusual

FIG. 3.—Curves of red corpuscle diameters in case of Addison's anaemia, compared with normal, taken at interval of seven weeks. (J. W. Shackle and A. C. Hampson.)

degree of regenerative activity in the bone marrow in response to a toxæmia; they are consequently found in other severe toxic anaemias, such as lead poisoning.

In most cases the number of white corpuscles is reduced. This is due to the fact that the number of polymorphonuclear cells produced by the poisoned bone marrow is diminished. The lymphocytes form in the lymphatic glands and elsewhere in normal numbers; consequently the leucopenia is accompanied by relative, though not absolute, lymphocytosis.

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In the exceptional cases, in which an early diagnosis is made owing to the presence of subacute combined degeneration of the cord or of Hunter's glossitis suggesting the possibility of Addison's anaemia, or when the discovery of achlorhydria in a case of gastric or intestinal dyspepsia is followed as a routine measure by a complete blood examination, the blood picture generally presents some at any rate of the features which are characteristic of the fully developed disease, even if the degree of anaemia is very slight or actually non-existent.

Thus in one of my cases of subacute combined degeneration of the cord the patient had achlorhydria. He did not look pale, and on December 12th, 1922, his red corpuscles numbered 5,600,000 per c.mm., his haemoglobin percentage being 85. But, although the colour index was only 0.76, the average size of his red corpuscles was increased from the normal of 7.22μ to 8.86μ , and well marked anisocytosis was present, the Price-Jones chart of his red cells being quite typical. Nine weeks later, on February 25th, 1923, the haemoglobin percentage had fallen to 46, and the red corpuscle count to 2,500,000 per c.mm., the serum was yellow, and van den Bergh's test, which was negative at first, gave an indirect positive reaction. After this, however, steady improvement occurred, and by April 8th the haemoglobin percentage had risen to 86 and the red corpuscle count to 4,500,000 per c.mm.

THE CAUSE OF THE ANAEMIA.

The observations of William Hunter,³ begun in 1886, proved that Addison's anaemia is caused by excessive blood destruction, which leads to the deposition of excess of iron-containing pigment in all the viscera.

It has long been known that the blood serum in Addison's anaemia is definitely yellow, whilst that in non-haemolytic anaemias is nearly colourless. Hijmans van den Bergh² has shown that this colour is due to excess of bilirubin in the blood. The depth of the colour and the degree of van den Bergh's "indirect" reaction for bilirubin in the blood are a measure of the activity of haemolysis.

The characteristic lemon colour of the skin in Addison's anaemia is a less intense colour and is of a different tinge from that of even very slight obstructive jaundice, in spite of the high concentration of bilirubin in the blood. Only if the hyperbilirubinaemia exceeds the leakage point and bile appears in the urine, as may happen in the acute haemolytic crises which often occur in the course of the disease, does actual jaundice with discoloration of the conjunctivae occur. Van den Bergh has shown that bilirubin is altered in certain of its properties after excretion in the bile, so that any bilirubin which is reabsorbed can be distinguished from that which has never left the blood stream. It is thus possible by means of van den Bergh's reaction to distinguish hyperbilirubinaemia caused by haemolysis from that caused by reabsorption of bile in obstructive jaundice, even if the latter is so slight or the examination is made at such an early stage that no bile has yet appeared in the urine and jaundice has not developed. The lemon-yellow colour of the skin in Addison's anaemia is probably caused by staining with bilirubin, which has not yet undergone the changes in its characters which excretion into the bile brings about. Bilirubin reabsorbed after these changes have occurred leads to the skin and conjunctivae becoming stained the familiar colour of ordinary jaundice.

ACHLORHYDRIA IN ADDISON'S ANAEMIA.

Since 1897, when Martius⁶ first drew attention to the absence of free hydrochloric acid from the gastric contents in Addison's anaemia, it has gradually become recognized that the association is almost, if not quite, invariable. Thus Ewald,⁷ using the old-fashioned test meal, found achlorhydria in every one of 75 cases; Zadek⁸ obtained the same result in 50 cases, and according to Weinberg⁹ it was present in every one of the 105 cases of Addison's anaemia in Martius's clinic at Rostock between 1900 and 1917. Levine and Ladd,¹⁴ using an Ewald test meal and obtaining samples of the gastric contents whilst fasting and every three-quarters of an hour afterwards, found free hydrochloric acid only three times in a series of 108 cases. In one of the exceptions the blood picture and symptoms were typical of Addison's anaemia and the diagnosis was confirmed *post mortem*, but in the two others the diagnosis remained doubtful even at the autopsy.

Recent investigations with the fractional test meal have shown that the free hydrochloric acid is invariably absent throughout the whole period of digestion (Fig. 4). In other conditions, such as cancer of the stomach, it is not at all uncommon to find a small quantity of free acid and occasionally even a large quantity in one or more of the fractions when the resting juice and the contents removed at the end of three-quarters of an hour or an hour both contain none, but this is never the case in Addison's anaemia. Complete achlorhydria was present in every one of my 24 cases examined by the fractional method.

It is clear, therefore, that before a case can be diagnosed as Addison's anaemia in spite of the presence of free hydrochloric acid in the gastric contents the clinical and pathological features must be subjected to special scrutiny. Weinberg⁹ has reviewed all cases in which sufficient clinical

details were available and in which Addison's anaemia was diagnosed in spite of the presence of free hydrochloric acid in the gastric contents, and concludes that in every instance the diagnosis was doubtful.

Gastric analysis may give information of real help in diagnosis, the presence of free hydrochloric acid in any fraction of a test meal being a decisive point against Addison's anaemia, whereas the discovery of achlorhydria would considerably strengthen the probability of such a diagnosis being correct. At the autopsies on the only two cases in Guy's Hospital in which a diagnosis of Addison's anaemia had been made in spite of the fact that free hydrochloric acid was present in the stomach, no evidence of haemolysis was present; one patient was found to have infective endocarditis, and the other, who died of pneumonia, had the microscopical changes in the spleen typical of Hodgkin's disease.

It has been suggested that the achlorhydria is secondary to the anaemia. But there is abundant evidence that the achlorhydria precedes the development of the anaemia. There is generally a more or less long history of digestive disturbance, of the type which may result from uncomplicated achlorhydria, preceding the first symptoms of anaemia. One of my patients, for example, had suffered for fourteen years from intractable diarrhoea, which completely stopped directly he was given hydrochloric acid after our diagnosis of Addison's anaemia had led to the discovery of his achlorhydria. In two cases achlorhydria was actually discovered twelve years (Bie,¹⁰ Gross¹¹), in two others ten (Faber,¹² Wilkinson), and in others seven (Faber, Cobet and Morawitz¹³), six (Levine and Ladd¹⁴), five (Kuttner¹⁵), three (Faber, Wilkinson), two (Charles Hunter¹⁶), and one year (Levine and Ladd) before the onset of anaemia. In Faber's three cases the blood was examined when the achlorhydria was discovered; there was no sign of anaemia, and the haemoglobin percentage was 100, 95, and 90 respectively.

If achlorhydria were secondary to the anaemia, or even if it were secondary to gastritis produced by the same toxin which caused the anaemia, cases would occur in which normal gastric secretion could be observed giving place to hypochlorhydria and finally complete achlorhydria as the disease progressed. Such a sequence of events, for example, has been observed in cancer of the stomach. But achlorhydria is found in all cases of Addison's anaemia at whatever stage of the disease the examination is made, and no case has been recorded in which either a normal secretion or even hypochlorhydria has been discovered at one period and achlorhydria on a later occasion.

The achlorhydria persists when the anaemia has almost

FIG. 4.—Fractional test meal in case of Addison's anaemia. A represents total acidity; free HCl is absent, but B represents amount of N/10 HCl required to produce free acid. The shaded area represents the limits of free HCl in 80 per cent. of normal people.

or completely disappeared, either spontaneously or as a result of treatment. Thus in four cases at Guy's it was still present when the haemoglobin percentage was 85, 82, 80, and 100 respectively, compared with 45, 38, 23, and 46 respectively some months or years before. Still more remarkable is the case of a man, who seventeen years ago was in the London Hospital for typical Addison's anaemia with 700,000 red corpuscles per c.mm. and complete achlorhydria. The achlorhydria is still present, though for years he has been perfectly well; when shown recently before the Medical Society of London by Maitland-Jones,¹⁷ his red corpuscles numbered 5,200,000 per c.mm.

The achlorhydria is thus far more constant than any other symptom, not excluding the anaemia. Even the anisocytosis and increase in the average size of the red corpuscles may in rare instances disappear completely during remissions and after apparent recovery, though the achlorhydria persists.

There is no constant change in the gastric secretion in any other form of anaemia. Thus fractional test meals in four consecutive cases of gastric or duodenal ulcer, complicated by severe secondary anaemia due to haemorrhage, gave curves of exactly the same form as would have been expected in the absence of haemorrhage; the percentage of haemoglobin was 30, 33, 48, and 49, figures which are quite as low as one would expect to find in an average series of cases of Addison's anaemia when first examined (Fig. 5). In two cases recorded by Campbell and Conybeare¹⁸ of secondary

FIG. 5.—Fractional test meals, showing curves of free HCl in three cases of secondary anaemia with 30, 33, and 48 per cent. haemoglobin respectively.

haemoglobin percentage was 25 and 17 on two occasions three months and three weeks respectively before death; a test meal given the same day as the first count and again a week after the second showed that free hydrochloric acid was present, though in small quantities. It is obvious, therefore, that anaemia does not cause achlorhydria.

There is, I believe, nothing specific about the achlorhydria which is an essential predisposing cause of Addison's anaemia. It is in most cases caused by constitutional and congenital absence of gastric juice—achylia gastrica—in which no hydrochloric acid and very little or no pepsin are secreted, but it may also be caused by acquired achylia and by any condition in which such acid as is secreted is at once completely neutralized.

1. Constitutional Achylia Gastrica and the Familial Occurrence of Addison's Anaemia.

Martius in 1897 expressed the belief that the majority of cases of achylia gastrica are primary or constitutional, and that comparatively few cases are secondary to some local disease, such as gastritis or cancer. Fragments of mucous membrane, which I have had removed during an operation for appendicitis in patients with achlorhydria, have generally looked perfectly normal and have always shown the usual number of healthy living oxyntic cells.

Constitutional achlorhydria is probably due to an inborn deficiency in the functional capacity of structurally normal gastric glands. In favour of this view is its occurrence in different members of the same family. Thus Albu¹⁹ discovered it seven times in more than one member of a family, and it was present in two out of three sisters who consulted me at different times on account of slight digestive symptoms.

There is some evidence that the constitutional incapacity of the gastric glands to secrete hydrochloric acid is congenital. Thus it was already present in 4 per cent. of the hundred medical students examined by Bennett and Ryle²¹

and the fifty examined by Campbell, the age of the majority being about 19 or 20. Albu has observed achylia gastrica in thirty-one children less than 10 years old, the youngest being only 4, and among the families of patients with Addison's anaemia examined by Weinberg were children with achylia aged 3, 4, 5, 6, and 10 (two). The children had been brought to Albu on account of anorexia, feeble development, or diarrhoea. On the other hand, the children examined by Weinberg were quite healthy, and their gastric secretion was only investigated because one or other parent had Addison's anaemia and achlorhydria.

Congenital achylia gastrica is the inherited factor in the cases of familial Addison's anaemia, which have been recorded with increasing frequency since Gulland²² first drew attention to the subject in 1907. Such familial cases have been recorded by Gulland and Goodall,²³ Gilbert and Weil,²⁴ Patek,²⁵ Bartlett,²⁶ Matthes,²⁷ Roth,²⁸ Levine and Ladd (nine),¹⁴ Cabot (two),²⁹ Schauman (seven),³⁰ Mustelin,³¹ Hastings Gilford,³² and Professor Houston of Belfast (three); the number in a family was in one case six, in one five, in four four, in three three, and in the rest two.

Still more important are the cases in which various members of the same family of a patient with Addison's anaemia are found to have achlorhydria, though apparently in perfect health. Such families have been described by Martius,⁶ Queckenstedt,³³ Faber,¹² and Schauman.³⁰ Weinberg⁹ examined the gastric contents of twenty-two children and two sisters of twelve patients with Addison's anaemia and achylia gastrica in Martius's clinic. Nine of the children and one sister of seven of the twelve patients had achlorhydria. The most striking history was that of a man with Addison's anaemia, who had four children; of these a boy of 10, a boy of 6, and a girl of 4 had achlorhydria. At this early age it is obvious that the abnormality must have been constitutional and congenital and not acquired.

A lady of 54 recently came under my observation for pyelitis. Hearing that her sister had died at the age of 36 of Addison's anaemia, we gave her a fractional test meal, although she had had no digestive symptoms except a prolonged attack of diarrhoea some years before. We found she had complete achylia. This was doubtless a familial abnormality, predisposing to Addison's anaemia in her sister and perhaps to the diarrhoea in herself.

The majority of people with constitutional achylia gastrica are none the worse for it, beyond being subject to attacks of indigestion, and especially nausea and diarrhoea, which quickly improve with the administration of dilute hydrochloric acid. Some probably pass through life without even suffering from any digestive symptoms. In others the achylia appears to predispose to the development of cholecystitis, appendicitis, and rheumatoid arthritis. In a small proportion of cases the other factors appear, which lead to the development of Addison's anaemia.

According to the statistics of the Registrar-General for 1921, about 9,000 per million of the population in Great Britain over the age of 20 die annually, and of these 65, or 0.7 per cent., die of Addison's anaemia. The number of cases erroneously diagnosed as Addison's anaemia is probably no greater than that of cases in which the disease is mistaken for some other condition such as cancer. If it be accepted that about 4 per cent. of all adults have achlorhydria, it is also presumably present in 4 per cent. of those who die. As the proportion of cases in which the achlorhydria, which is followed by Addison's anaemia, is acquired and not constitutional is probably very small, it follows from these statistics that about one in six, or 16 per cent., of individuals with constitutional achlorhydria ultimately develop Addison's anaemia.

2. The Connexion of Chronic Gastritis and Atrophy with Achlorhydria and Addison's Anaemia.

Samuel Fenwick³⁴ in 1877 observed that the mucous membrane of the stomach was markedly atrophied *post mortem* in some cases of Addison's anaemia, and in recent years Faber has upheld the view that achylia gastrica, including that which is associated with Addison's anaemia, is always due to gastritis. But the pathological changes in the stomach in achylia gastrica are often so slight and

patchy, large areas with normal glands being present, that the achylia cannot be due to actual destruction of all the secreting tubules.

The origin of the gastritis can, I believe, be best understood by a consideration of the functions of the gastric juice. Quite apart from its specific activities, the gastric juice softens any hard and dry particles of food which reach the stomach as a result of insufficient mastication, and dilutes such chemical irritants as alcohol which may reach it in a too concentrated form. The achylia gastrica, which is an inborn error of function, unconnected with any organic change in the stomach, is thus likely sooner or later to be complicated by chronic gastritis. As it frequently gives rise to no symptoms of any kind, the individual receives no warning that he must be exceptionally careful to chew his food thoroughly, to avoid mechanical and chemical irritants in his diet, and to avoid swallowing very hot or very cold food or drink. In many cases the chronic gastritis produced in this way is complicated by an infective gastritis caused by invasion of the mucous membrane by streptococci from the mouth, which would have been destroyed by the acid of the gastric juice in normal individuals. By the time that obvious symptoms have developed, and still more so by the time that death occurs from some secondary or independent disease, the gastric mucous membrane may show definite changes. If the achlorhydria were secondary to the gastritis, secretion of gastric juice would return when the gastritis disappeared as a result of treatment. But this never occurs.

3. Achlorhydria of Alcoholic Gastritis and Cirrhosis of the Liver.

I have seen one case of alcoholic cirrhosis of the liver associated with Addison's anaemia. The patient had symptoms of chronic gastritis, and a fractional test meal showed that complete achlorhydria was present. In my experience cirrhosis of the liver is generally accompanied by complete achlorhydria, secondary in all probability to the alcoholic gastritis, as I have watched the return of a normal curve of secretion during treatment by careful dieting and complete abstention from alcohol. It is probable, therefore, that when Addison's anaemia develops in a patient with alcoholic cirrhosis of the liver, the achlorhydria, which is an essential factor for its development, is secondary to the alcoholic gastritis and is not primary and constitutional. If the patient could be persuaded to abstain permanently from all alcoholic drinks, the return of normal gastric acidity would render the prognosis unusually hopeful.

4. Achlorhydria after Gastro-enterostomy and Gastrectomy.

In one of the Guy's series of cases Addison's anaemia followed gastro-enterostomy. Except when performed for duodenal ulcer this operation is frequently followed by complete achlorhydria owing to the rapid drainage of the stomach and the neutralization of the gastric juice by the alkaline fluids entering through the stoma from the proximal loop of jejunum (Conybeare³⁵). Achlorhydria acquired in this way probably provided the essential predisposing cause for the development of the anaemia.

Hartman³⁶ records the case of a man, aged 58, in whom W. J. Mayo excised the whole stomach for carcinoma. At that time his red blood corpuscle count was 5,520,000 per c.mm. He did very well for about a year, but then became progressively weaker and more anaemic. Twenty months from the date of operation his red count was 2,000,000 per c.mm., the haemoglobin percentage was 53, and the colour index 1.3; there was slight anisocytosis and poikilocytosis. A year later he was still weaker, and his blood showed similar but more severe changes. Thus a patient, who had been completely deprived of gastric juice by the removal of his stomach, developed within a couple of years the blood picture of Addison's anaemia, which Hartman also regards as invariably associated with achlorhydria. He suggests that the characteristic picture of Addison's anaemia might have been discovered if a blood examination had been performed on Moynihan's³⁷ patient, who died from severe anaemia of less than twelve

months' duration, three years and eight months after complete gastrectomy for cancer, without any abnormality being found at the autopsy. Dr. J. R. Bell tells me of three other cases of Addison's anaemia which followed the artificial achylia produced by total gastrectomy performed for cancer in Vienna.

5. The Achlorhydria of Gastric Cancer and Addison's Anaemia.

In 50 per cent. of cases of gastric cancer complete achlorhydria is found with the fractional test meal, and oral sepsis is, of course, not uncommon. The conditions required for the development of Addison's anaemia and subacute combined degeneration of the cord may therefore be present in cancer of the stomach. In a case of typical subacute combined degeneration of the cord recently under my care, with the characteristic blood picture of Addison's anaemia, complete achlorhydria, and glossitis, a tumour was felt under the left costal margin, and each fraction of the test meal contained obvious blood. After his very septic teeth had been extracted, an exploratory laparotomy was performed and revealed an inoperable growth of the stomach. The patient died ten days later, about a year after the first appearance of nervous and digestive symptoms. It seems very probable that the achlorhydria was secondary to the growth of the stomach, and that this allowed the intestine to become infected from the mouth and so led to the development of neurotoxic and haemolytic poisons.

DEGENERATION OF THE SPINAL CORD IN ADDISON'S ANAEMIA.

In the last twenty-five years spinal cord symptoms have been recognized in Addison's anaemia with increasing frequency as they have become more systematically looked for. Thus in 1918 Woltmann³⁸ found "indisputable evidence of the destruction of nervous parenchyma" in 80.6 per cent. of 150 cases, which were subjected to a detailed neurological examination at the Mayo Clinic. This corresponds closely with my own experience, and with the figures obtained by Minnich,³⁹ who discovered degenerative changes in 77 per cent. of the spinal cords of a consecutive series of fatal cases of "pernicious" anaemia.

I believe that no definite line can be drawn between Addison's anaemia accompanied by changes in the spinal cord, and subacute combined degeneration of the cord accompanied by anaemia. The difference is simply one of degree, and depends upon whether a haemolysin or a neurotoxin is the more active. If either toxin is first produced alone, there is more time for it to give rise to marked changes; thus when Addison's anaemia is rapidly fatal there may be no time for nervous symptoms to develop, or, if they do develop, they may be trivial in comparison with those observed in cases in which the nervous degeneration has progressed for many months without any anaemia. There appears to be no essential difference between the clinical symptoms or the pathological changes in the spinal cord except in their severity, whether the nervous degeneration or the anaemia predominates.

NATURE OF THE ANAEMIA ASSOCIATED WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

In some of the nine cases reported by Risien Russell, Batten, and Collier⁴⁰ in 1900, in their classical description of subacute combined degeneration of the cord, no anaemia was recognized throughout the disease; in others it developed towards the end, whilst in others it preceded the manifestation of nervous symptoms by many months. They stated that repeated examinations of the blood "failed to reveal the alterations found in pernicious anaemia," the changes being those characteristic of secondary anaemia. However, in his latest article on the subject, published in 1921, Collier⁴¹ states that a careful investigation of the blood changes at various stages of the disease and of *post-mortem* findings in a large series of cases has convinced him that the blood changes in every case are identical with those met with in the various stages of Addison's anaemia, and that the typical *post-mortem* picture of the disease occurs frequently in subacute combined degeneration.

Our experience⁴² entirely agrees with that of Bramwell and Collier. The anomalous results obtained on examination of the blood in many cases is due to the fact that the blood picture of Addison's anaemia in its most characteristic form is only present when the anaemia has attained a moderately severe degree. In the early stage of blood destruction, which is rarely recognized in uncomplicated cases of Addison's anaemia, but is that which is most frequently present when a case of subacute combined degeneration first comes under observation, the picture is far less characteristic. The colour index is often under 1, nucleated red corpuscles are rarely present, but there is always some anisocytosis, and in the five cases of our series in which Price-Jones' curves were charted, the result obtained was typical of Addison's anaemia. Moreover, the blood serum was abnormally pigmented, and van den Bergh's indirect reaction for bilirubin was positive.

The lemon-yellow colour, which Collier observed in many cases before he came to the conclusion that the anaemia was of the "pernicious" type, is quite characteristic of the latter, and affords just as good evidence of haemolysis as the Prussian-blue reaction obtained in the liver and sometimes in other organs after death. This reaction, although present in almost all cases of typical Addison's anaemia, is sometimes absent in subacute combined degeneration, because the blood destruction has not been sufficiently severe and prolonged.

ACHLORHYDRIA IN SUBACUTE COMBINED DEGENERATION OF THE CORD.

J. R. Bell and I⁴² have had the opportunity of investigating twelve cases of typical subacute combined degeneration of the cord by the fractional method of gastric analysis. In all of the twelve free hydrochloric acid was completely absent throughout the period of digestion. Dr. J. F. Wilkinson of Melbourne informs us that he discovered achlorhydria in a patient who consulted him for digestive symptoms a year before the first signs of subacute combined degeneration of the cord appeared, and Szlapka⁴³ has described a similar case in which the interval was two years.

For purposes of control gastric analyses were made by Bell in a series of typical cases of disseminated sclerosis and tabes dorsalis. In eight consecutive cases of disseminated sclerosis achlorhydria was never found, the curves of acidity being the same as would be likely to occur in a series of eight normal people. Of nine consecutive cases of tabes dorsalis one was found to have achlorhydria. The remainder had curves which fell within normal limits, though in two cases it was somewhat high. As 4 per cent. of normal individuals have achlorhydria the single case in this series is probably of no importance (Table I).

TABLE I.—Results of Fractional Test Meals in Various Conditions.

	Number of Cases.	Achlorhydria.		Low Acidity.	"Normal" Acidity.	High Acidity.
		Number.	Per-centage.			
Normal (Bennett and Ryle ²¹)	100	4	4	1	27	8
Various medical diseases (Bell) ⁴⁴	425	63	14.8	53 (12.5 %)	205 (48.3 %)	104 (24.4 %)
Carcinoma of stomach	13	6	46	4	3	0
Addison's (pernicious) anaemia	24	24	100	0	0	0
Subacute combined degeneration of cord	12	12	100	0	0	0
Tabes dorsalis ...	9	1	11	1	5	2
Disseminated sclerosis	8	0	0	1	7	0

The diagnosis in doubtful cases may be greatly helped by gastric analysis. The presence of free hydrochloric acid in any fraction of a test meal is a very strong point against the diagnosis of subacute combined degeneration, whereas the discovery of achlorhydria greatly strengthens the probability of such a diagnosis being correct. In three

recent cases, which presented features very suggestive of subacute combined degeneration, a normal curve of gastric acidity was discovered. Each eventually proved to be a case of syphilitic disease of the spinal cord.

It has been stated that severe cachexia, as well as Addison's anaemia, may be associated with similar changes in the spinal cord, but we have been unable to find any detailed description of such cases, the majority of which appear to have been due to cancer of the stomach. I have, however, already referred to a case of my own, in which subacute combined degeneration and Addison's anaemia developed in a patient with cancer of the stomach. The achlorhydria resulting from the latter was probably the cause of the intestinal infection, which led to the spinal degeneration and the Addisonian anaemia.

It has generally been stated that subacute combined degeneration of the cord may occur without any anaemia. We have, however, seen no reports of such cases in which blood examinations have been made during the last two or three weeks of life, and Byrom Bramwell's⁴⁵ case, in which anaemia of a typical Addisonian form developed during the fortnight before death shows how necessary it is to do this before concluding that the nervous disease runs its whole course without being complicated by anaemia. I have already mentioned a case in which an acute haemolytic crisis lasting three months occurred in a man suffering from subacute combined degeneration of the cord, whose haemoglobin percentage was 85 before and 100 after the crisis, though the lowest point it reached during the crisis was 46. It would, however, not be surprising if in a small proportion of cases no anaemia occurred at all, because there is no reason why in some cases a neurotoxin might not be produced without a haemolysin, just as the latter are certainly produced in a considerable number of cases without the former.

It is interesting to note that cases of subacute combined degeneration occur with a family history of Addison's anaemia. Thus the father, paternal grandfather, paternal uncle, and brother of a male patient of mine with the nervous disease, achlorhydria, and anaemia, died of the anaemia. But fortunately the three children of the patient had normal gastric secretion, so that there is no reason why they should inherit the disease. The grandfather of another male patient of mine died of Addison's anaemia, and Willson⁴⁶ has recorded the case of a woman with the nervous disease whose two maternal aunts died of the anaemia.

ORAL SEPSIS AND GLOSSITIS IN ADDISON'S ANAEMIA.

In 1900 Hunter³ introduced the now familiar term "oral sepsis" to describe the infective condition of the mouth, which is an undoubted factor in the pathogenesis of numerous diseases, and demonstrated for the first time the extreme importance of its association with Addison's anaemia. Improved methods of investigation, and especially radiography, have only confirmed the views he expressed nearly a quarter of a century ago. It has sometimes been said that the occurrence of Addison's anaemia in edentulous patients proves that the association with oral sepsis is not invariable, but the vast majority of edentulous patients are only edentulous because they have had severe oral sepsis, and the latter may have laid the foundations of the disease before the teeth were extracted, even if a considerable interval elapsed before its presence became obvious. Moreover, there are other sources of sepsis, such as the tonsils and nasal sinuses, which may in exceptional cases provide an alternative primary focus of infection. I have never myself seen a case of Addison's anaemia or subacute combined degeneration of the cord in which evidence of oral and in exceptional cases pharyngeal sepsis could not be found on careful investigation.

The sore tongue, which is now widely recognized as a very common symptom of Addison's anaemia, was described by William Hunter in 1839, and in the thirty-four years which have since elapsed he has repeatedly directed attention to it as an essential feature of the disease, which he has seen in every case—150 or more—of which he has full records. I have, however, certainly seen one fatal case in which soreness of the tongue had never been present and in

which its appearance remained perfectly normal throughout the illness.

Hunter believes that the characteristic glossitis is secondary to the oral sepsis, the infection spreading in most cases from septic teeth to the neighbouring part of the tongue. The glossitis thus produced may be the focus from which the intestines are subsequently infected, if the teeth are removed before the disease has developed, as there is often a history of recurrent attacks of soreness of the tongue before the onset of symptoms due to the anaemia. In two patients of Schauman's the glossitis preceded the discovery of anaemia by five and ten years respectively.

The patient complains of soreness of the tongue, which is increased by highly seasoned food and by hot food and fluids, so that he cannot eat or drink anything which is not cold. The soreness may amount to actual pain. Red patches appear, especially at the tip and edges, and small vesicles may form. The glossitis varies greatly in degree from time to time, and the acute inflammation with its accompanying soreness may disappear completely for long periods, being sometimes present only for a few days or weeks at a time. In quiescent periods evidence of past glossitis may be afforded by fissures or by smooth patches, from which the papillae have more or less completely disappeared.

Familiarity with the characteristic features of the glossitis of Addison's anaemia may make it possible to diagnose a case before the symptoms caused by the anaemia have appeared. I was recently consulted by a lady on account of soreness of her tongue, the appearance of which was so suggestive of Hunterian glossitis that a complete investigation was carried out and revealed the presence of blood changes typical of Addison's anaemia together with complete achlorhydria, and Dr. R. D. Passey has told me of a similar case under his care.

According to Hunter the glossitis is quite specific, and occurs in connexion with no other disease. But I have seen glossitis identical in appearance with that occurring in Addison's anaemia in at least three cases of severe, but not haemolytic, anaemia, one of which was secondary to cancer of the colon, so I cannot regard the presence of a sore tongue in an anaemic patient as conclusive evidence that the anaemia is of the Addisonian type.

THE EVIDENCE OF INTESTINAL INFECTION IN ADDISON'S ANAEMIA AND SUBACUTE COMBINED DEGENERATION OF THE CORD.

In 1889 Hunter suggested for the first time that Addison's anaemia is due to excessive destruction of blood caused by the absorption of haemolytic poisons from the alimentary tract; he thought that these poisons were produced in specific lesions affecting particularly the tongue and stomach, but also the intestine. His own later investigations and those of many other observers have confirmed his main thesis that a haemolytic toxin is produced in the digestive tract. But whatever we may conclude as to the significance of the specific glossitis he described, there seems little doubt that any gastritis present is secondary to the achlorhydria, which is a constant predisposing factor and is in most cases constitutional and congenital in origin. The observations which I shall now describe show, I believe, that a definite infection of the intestine with a haemolytic streptococcus is present in Addison's anaemia, but Faber and Bloch, using improved methods to prevent *post-mortem* changes, found that it was not, as was formerly believed, associated with any inflammatory or atrophic lesion of the intestinal mucous membrane.

Streptococci are almost invariably present in the sockets of septic teeth, whether the individual is otherwise healthy or not. But so far as our observations go the *Streptococcus longus* is not often found in the contents of the duodenum removed during life with an Einhorn tube, except in Addison's anaemia and in subacute combined degeneration of the cord. In four normal individuals and in eight cases of infective jaundice from Gallipoli investigated by me with C. J. Martin in Lemnos in the autumn of 1915, no streptococci were present. Among 56 patients suffering from various other conditions the duodenal contents contained

the *S. longus* in only nine instances, and in these they were generally very scanty and slow growing. In seven of the 56 cases achlorhydria was present, together with very severe oral sepsis in two and slight pyorrhoea alveolaris in three, but in spite of this no streptococci were found. In every one of the ten cases of Addison's anaemia and the five cases of subacute combined degeneration of the cord which we have investigated the *S. longus* was found on cultivation of the duodenal contents. In the more recent cases F. A. Knott has investigated the haemolytic power of the streptococci; he found that they were always haemolytic in the anaemia cases, but never in the others.

The contrast between the 10.9 per cent. of controls in which streptococci were found with 100 per cent. of patients with Addison's anaemia and subacute combined degeneration of the cord is so striking that it is, I think, fair to conclude that an infection of the intestine with a haemolytic *Streptococcus longus* is an essential factor in the production of these diseases. In any case, the presence of the *S. longus* in the duodenum is evidence of active infection of the intestine. In two of my patients with subacute combined degeneration of the cord an autogenous vaccine made from the *S. longus* isolated from the socket of an infected tooth gave rise to a temporary aggravation of the sensation of pins and needles in their hands and feet each time it was injected, but this was followed eventually by the almost complete disappearance of the symptom.

A small number of observations on the bacteriology of the duodenum have been published since our first communication on the subject, and they confirm our results. Thus in fourteen normal individuals examined by Bogendörfer⁴⁷ the contents, though not sterile, contained neither *B. coli* nor streptococci. In four out of six patients with hyperchlorhydria examined by Gorke the duodenal contents were sterile, and in the remaining two a very small number of organisms were found. On the other hand, in seven cases of achlorhydria examined by Gorke⁴⁸ and eleven by Bogendörfer large numbers of bacteria were always present; in the majority of cases these included *B. coli*, but the *S. longus* was not found. In the only two cases of Addison's anaemia investigated a haemolytic streptococcus was isolated by Bogendörfer in addition to the bacteria found in the other cases.

I believe that the reason why achlorhydria is an essential predisposing cause of Addison's anaemia and subacute combined degeneration of the spinal cord is because the loss of the antiseptic action of the normal gastric juice alone makes it possible for the bacteria, which reach the stomach from the mouth when oral sepsis is present, to infect the intestine. But the association with oral sepsis with achlorhydria only leads to the development of Addison's anaemia when the sepsis is due to infection with a special streptococcus, which produces haemolytic and neurotoxic poisons when it has established itself in the small intestine. Knott has recently made the important observation that dilute hydrochloric acid exerts a much more powerful bactericidal effect on streptococci than on other organisms, such as *B. coli* and staphylococci.

In addition to the bacterial toxins it is possible that others are produced by the action of the organisms on the proteins, which reach the duodenum in a completely undigested form owing to the absence of the normal digestive activity of the gastric juice.

In whatever way the poisons are produced it is probable that one of them is specially toxic for the blood and leads on absorption to a haemolytic form of anaemia, and that another is specially toxic for nervous tissues and leads to combined degeneration of the spinal cord. In most cases the former toxin is the dominant one, but in a small minority of cases the latter is the more important. Although one or other may appear to be present alone in the early stages, it is rare for the haemolytic toxin, and still more rare for the neurotoxin, to be produced without the other throughout the course of the illness.

REMISSIONS.

One of the most remarkable features of Addison's anaemia is the frequency of remissions, during which the patient feels perfectly well. A slightly lemon-yellow colour may

still be detected in his skin, but he no longer looks abnormally pale. The spleen is generally still palpable, and gastric analysis shows that complete achlorhydria is present. In a large majority of cases the blood picture is still abnormal. The colour index remains over 1, though the number of red corpuscles may be nearly normal and the haemoglobin percentage exceed 100. The average size of corpuscles remains greater than normal and definite anisocytosis is present, but no nucleated cells or poikilocytes are found, and van den Bergh's reaction is either very faint or completely absent. In very exceptional cases the blood picture is normal or shows nothing more than a slight anaemia of a secondary type.

In remissions, in which the blood picture still shows some of the characteristics of Addison's anaemia, toxins are probably still being produced and slight blood destruction is still occurring. In the remissions, in which the blood picture is normal, there is probably no toxæmia; consequently no excessive haemolysis occurs and blood formation in the bone marrow takes place in a normal manner. Unfortunately these cases tend to relapse almost as surely as those in which blood destruction and pathological activity of the bone marrow have never ceased.

Zadek³ has found by examining a specimen of bone marrow removed from the middle of the tibia that the red marrow with its preponderance of megaloblasts, which is always found in fatal cases of Addison's anaemia, is present during life in the active stages of the disease, but is replaced by normal yellow marrow, containing mainly fat cells with a few normocytes and only a very small number of megaloblasts, during remissions, whether these are associated with a blood picture which is still abnormal or with one which is normal in every way. It is clear, therefore, that Ehrlich's theory that Addison's anaemia is a primary megaloblastic degeneration of the bone marrow is incorrect. The changes which occur in the marrow are secondary, and result from an attempt to compensate for the prolonged and excessive blood destruction, being analogous to the changes which occur in anaemia following severe haemorrhage, and perhaps also in part from reaction to the same toxin which produces the haemolysis. Sometimes in the early stages, and in rare cases during remissions, the blood picture shows none of the changes which result from the reaction of the bone marrow, although some anaemia may be present, which van den Bergh's test shows is haemolytic in character. The characteristic features of the blood in Addison's anaemia are due to the reaction of the bone marrow to the toxæmia, and the stage when it appears and its degree at any period depend upon the varying power of reaction of the marrow in different individuals. Remissions are caused by partial or complete cessation of the toxæmia, and not, as has often been maintained, by the megaloblastic regenerative activity of the marrow, which Zadek's observations on the bone marrow have shown is no more manifest during remissions than it is in normal individuals. The occurrence of remissions in which the blood picture is perfectly normal confirms this view.

I believe that the partial or complete disappearance of toxæmia which results in remissions is brought about by the development of a certain degree of immunity towards the infection, this originating either spontaneously or, more commonly, as a result of treatment, which has led on the one hand to a diminution of the virulence of the infection, and on the other to greater resisting power of the patient as a result of improvement in the anaemia brought about by the administration of arsenic and by transfusion. The almost inevitable relapse occurs because the infection has not been completely overcome, and because the achlorhydria—the essential predisposing cause—is permanent and unaffected by the general improvement. A remission can only pass into complete recovery if the intestinal infection is annihilated and the primary source of infection is completely and permanently eradicated. The achlorhydria then would no longer matter any more than it does in the large majority of other individuals who have constitutional achylia gastrica. Remissions in Addison's anaemia are thus strictly analogous to those in duodenal ulcer in which the predisposing hypersthenic stomach is also constitutional.

TREATMENT.

The Intestinal Infection.

The most important part of the treatment of Addison's anaemia and subacute combined degeneration of the cord is to overcome the intestinal infection and so arrest the development of the neurotoxic and haemolytic poisons. Oral sepsis should be thoroughly dealt with, as Hunter first demonstrated in 1900. Every tooth which shows the slightest sign of infection on expert clinical examination should be condemned. An x-ray photograph should be taken of all the remaining teeth, however healthy they may appear, and the least evidence of apical infection or periodontitis should lead to their removal. In most cases every tooth will have to be extracted. If the tonsils are infected they must be enucleated; it should be remembered that infected tonsils are not necessarily large, and that severe infection in a flat tonsil may be hidden behind the anterior pillars of the fauces. Chronic nasal catarrh and infection of the nasal sinuses should also be looked for, and, if discovered, thoroughly treated. As the removal of infected teeth or tonsils is sometimes followed by an acute haemolytic crisis and aggravation of the nervous symptoms owing to the sudden absorption of large quantities of toxin from the raw surfaces, it is wise to give two or three injections of streptococcal vaccine prepared from the teeth and tonsils before removing them.

The achlorhydria should be corrected by the administration of large doses of dilute hydrochloric acid. The dose

usually given is quite insufficient. Anything less than a drachm of dilute acid given as a single dose during a fractional test meal does no more than barely neutralize the alkaline gastric contents for a quarter of an hour. At least a drachm and a half are required to produce anything like the normal acidity throughout the period of digestion of a test meal (Fig. 6), and two drachms or more

FIG. 6.—Fractional test meals to show free HCl in a man with subacute combined degeneration of the spinal cord. A, without addition of acid—complete achlorhydria; B, with addition of 5j dilute HCl (0.5 per cent. HCl) taken with the gruel—complete achlorhydria; C, with addition of 5iss dilute HCl in 3vj of water—normal curve; D, with addition of 5j dilute HCl in 3viij water—hyperchlorhydria curve. The shaded area represents the limits for free HCl of 80 per cent. of normal people.

are required for an ordinary meal. As Knott has shown that even a trace of free hydrochloric acid is strongly bactericidal for streptococci, the exact strength of the acid is comparatively unimportant. Pepsin is also very deficient or absent, so a grain should be added to each drachm of dilute acid in order to improve the gastric digestion. About 6 drachms of the acid should be mixed with a pint and a half of water, to which sugar and the juice of three oranges or two oranges and one lemon are added. The mixture makes a very palatable beverage, about one-third of which the patient should drink just before and during lunch, another third before and during dinner, and the rest fasting in the morning about an hour before breakfast. This first dose is probably the most important, as the acid can then act on the bacteria in the stomach and duodenum in a concentrated form, undiluted by food. If there is any difficulty in taking the acid it may be diluted by the addition of more water. The patient should continue to take it without intermission for the rest of his life, as, even if the intestinal infection appears to be overcome, the achlorhydria remains permanently in the large majority of cases.

Milk, which has been soured with an active lactic acid bacillus, should be given. It is best taken between meals so as not to be rendered inactive by the hydrochloric acid. Most patients can manage half a pint three times a day without difficulty. Though this remedy has lost much of the popularity it had a few years ago, there is no doubt

that it is a very efficient means of rendering the intestine a less suitable culture medium for most pathogenic bacteria.

Finely powdered or granulated charcoal absorbs gas in the intestines and is the best remedy I know for intestinal flatulence. It also makes the foulest stools almost odourless. It seems reasonable to suppose that it may also absorb some of the haemolysin and neurotoxin produced in Addison's anaemia. I therefore give a large tablespoonful of charcoal first thing in the morning and last thing at night.

As it is very probable that the haemolytic streptococcus, which can be isolated from the duodenal contents obtained through an Einhorn tube, is responsible for the toxæmia which causes Addison's anaemia, I advise the administration of an autogenous vaccine prepared from the patient's own duodenal haemolytic streptococcus, or, failing this, from a dental or tonsillar streptococcus. It should be given over a long period in doses so regulated as not to give rise to any general reaction.

The important part played by the spleen in the haemolysis of Addison's anaemia was proved by Hunter, who demonstrated the large amount of free iron it contained in fatal cases, and showed that splenectomy increased the power of animals to resist poisoning with such haemolytic toxins as toluylendiamine. Hijmans van den Bergh confirmed this by finding that blood removed from the splenic vein during splenectomy or after death in Addison's anaemia contained more bilirubin than the blood in the general circulation. It would therefore seem natural that splenectomy should be useful in Addison's anaemia, as it undoubtedly results in the removal of one of the sites of blood destruction. The results obtained in Addison's anaemia by splenectomy have not, however, in the past been sufficiently good to warrant the general adoption of the operation as a method of treatment. I believe that this is due to splenectomy having been tried independently of other methods of treatment. When employed in addition to the other treatment I have described it may prove to be of great value. Two patients of mine, who had shown no improvement for several weeks, and whose haemoglobin percentage would rise to 20 or just above after each transfusion, only to drop again to 15 a few days later, had their spleens removed by Mr. R. P. Rowlands and Mr. L. Bromley respectively. Though they had been delirious and extremely prostrate, they at once felt better after the operation, and the condition of their blood rapidly improved, so that both were able to leave hospital a few weeks later in definite remissions. All who had seen them during the weeks before the operations agreed that this improvement must almost certainly have been due to the splenectomy.

Symptomatic Treatment.

If the production of haemolytic toxins is arrested the blood shows spontaneous improvement. This may be greatly accelerated by symptomatic treatment. I need not say much about the treatment of the anaemia by arsenic, first introduced by Byrom Bramwell⁴⁹ in 1877, as it must be familiar to all of you. It should always be tried; in the majority of cases Fowler's solution given by mouth proves quite satisfactory, but occasionally some preparation which can be injected into the muscles or direct into the blood proves more efficacious.

Direct transfusion of blood was tried by Thomas Bryant in a case of Addison's anaemia at Guy's Hospital in 1879. I am convinced of the great value of this method of treatment, which generally requires repetition, often on several occasions. Experience shows that in many cases it not only adds a quantity of healthy blood plasma with normal red corpuscles to that already circulating, and in this way produces an immediate rise of 5 to 10 per cent. of haemoglobin, but it also frequently initiates a steady rise in the percentage, when this has been stationary or actually falling.

It might have been supposed that the cessation of toxæmia would not lead to any improvement in the nervous symptoms corresponding to that of the anaemia, although the progress of the spinal degeneration would be arrested. But I have seen considerable improvement result, not only in the sensory symptoms, but also in the ataxic paraplegia, quite apart from the result of treatment by re-education and exercises. This is probably due to the fact that the nervous tissue may be thrown out of action as a result of the toxæmia, but be still capable of recovering, if no more toxins are produced,

this being comparable with what occurs in various acute infective conditions involving the central nervous system. The degree of improvement which may occur depends therefore upon the amount of actual destruction of nervous tissue which is already present.

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TREATMENT OF TUBERCULOSIS OF THE URINARY TRACT.*

BY

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THE present century has witnessed a complete revolution in our ideas of the pathology and consequently of the treatment of genito-urinary tuberculosis. There are few of those present at this meeting who have not witnessed the use of a Volkmann's curette in the attempt to ameliorate a bladder lesion, an error indicative of the faulty pathological teaching of fifteen years ago. Progress in our conceptions of the disease is well shown by the attitude adopted at the congresses of urology held respectively in 1908 and 1913. At the former of these meetings the new teaching was in its infancy and on trial. It was accepted tentatively. The same subject was again set for discussion in 1913, and the general principles which guide us to-day were then established and accepted practically unreservedly.

The predominance of symptoms of cystitis, which is such a marked feature in this disease, was responsible for the view held previously—that the bladder was the organ primarily affected, and that the kidney became secondarily infected. This led to surgical energy being directed to the bladder instead of the kidney. Now we know that the kidney is primarily at fault, that almost invariably the disease is unilateral in its early stages, and that the bladder is affected secondarily. We know also that the other kidney will become affected in a very large proportion of cases, at a later date, and that if we remove the primarily involved organ the prognosis of the disease will be good, both as regards the bladder, which will heal, and as regards the other kidney, which is not very likely to become secondarily infected.

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