THE PATHOGENESIS OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD, WITH SPECIAL REFERENCE TO ITS CONNECTION WITH ADDISON'S (PERNICIOUS) ANÆMIA, ACHLORHYDRIA AND INTESTINAL INFECTION.

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SUBACUTE combined degeneration of the spinal cord has in the past been chiefly investigated by neurologists, who were only interested in a minor degree in the associated anæmia. On the other hand, the spinal changes observed in Addison's anæmia have been investigated chiefly by physicians, whose interest was in the anæmia rather than the spinal disease. The present paper is an attempt to discuss the two groups of cases from a common standpoint, and to show that both depend upon the same underlying pathological processes—oral sepsis, absence of free hydrochloric acid from the stomach contents throughout digestion, and consequent intestinal infection and intoxication.

The term Addison's anæmia is used in this paper instead of pernicious anæmia. Addison [1] first described the disease in 1847 and called it "idiopathic anæmia." Twenty years later Biermer published his work on the same subject and called the disease "pernicious anæmia." But beyond the pernicious name he invented, Biermer added little but confusion to our knowledge of the subject, and as the disease is neither idiopathic nor necessarily pernicious, there can be no doubt that "Addison's anæmia" is the most satisfactory name.

I.—THE PATHOGENESIS OF ADDISON'S ANÆMIA AND ACHLORHYDRIA.

Before considering the pathogenesis of subacute combined degeneration of the spinal cord, it is necessary to summarize the views we hold as a result of recent investigations on Addison's anæmia, particularly with regard to its association with achlorhydria. For the following

reasons we believe that the achlorhydria is an essential predisposing cause of the anæmia.

(1) There is abundant evidence that the achlorhydria precedes the development of the anæmia. As Robert Hutchison first pointed out in 1900, there is generally a more or less long history of digestive disturbances, of the type commonly associated with achlorhydria, preceding the first symptoms of anæmia. In one case achlorhydria was actually discovered twelve, in another ten, in another three years, and in another one year before the onset of anæmia.

(2) In sixty-four out of sixty-six fractional test meals carried out at Guy's and the London Hospitals on cases of Addison's anæmia complete achlorhydria occurred throughout the period of digestion. At whatever stage in the development of the anæmia the examination is made achlorhydria is found. It was present, for example, in cases in which the hæmoglobin percentage had not fallen below 85, 85, 80 and 68; it is thus a far more constant symptom than any other, even than the hæmatological signs, such as a high colour index and the presence of megaloblasts, as these are often absent in the early stages and even temporarily when the anæmia is severe.

(3) It persists when the anæmia has almost disappeared, either spontaneously or as a result of treatment. Thus in four cases it was still present when the hæmoglobin percentage was 85, 82, 80 and 70 respectively, compared with 45, 38, 23 and 53 respectively some months or years before.

(4) There is no constant change in the curve of secretion in any form of anæmia, except Addison's. Thus fractional test meals in our last four patients with gastric or duodenal ulcer, complicated by severe secondary anæmia due to hæmorrhage, gave curves of exactly the same form as would have been expected in the absence of hæmorrhage; the percentage of hæmoglobin in these cases was 30, 33, 48 and 49, which is quite as low as one would expect to find in an average series of cases of Addison's anæmia when first examined. In two cases of secondary anæmia caused by rectal hæmorrhage with a hæmoglobin percentage of 44 and 42 respectively, and in two cases of chlorosis with a percentage of 25 and 48, the curves of gastric secretion were normal. It is obvious, therefore, that anæmia does not cause achlorhydria.

(5) In a long series of cases it becomes clear that the achlorhydria is not specific, but that whatever its origin may be, it predisposes to the development of Addison's anæmia. Bennett and Ryle [5] have shown that about 4 per cent. of normal young men have achlorhydria. The history

in many cases of Addison's anæmia points to the achlorhydria being of this congenital type. In one it was due to alcoholic gastritis, in another it resulted from a gastro-enterostomy for ulcer, and—what proves conclusively that it is primary and not secondary—in at least five cases Addison's anæmia followed the artificial achylia produced by total gastrectomy performed for cancer. There is thus no constant pathological change, such as atrophy, in the gastric mucous membrane after death, and in one case of Addison's anæmia, in which a fragment was excised during an operation for appendicitis, Dr. R. D. Passey found no atrophy and no more inflammation than in a specimen obtained under similar circumstances in a case of "benign" achlorhydria.

For the above reasons we believe that Addison's anæmia only develops in individuals who have achlorhydria. The anæmia is caused by hæmolytic toxin absorbed from the intestine, where they have been produced by the action of bacteria coming originally from the mouth, the presence of achlorhydria having deprived the stomach of its antiseptic powers, which normally exert a powerful influence in protecting the bowel from such infection.

II.—DEGENERATION OF THE SPINAL CORD IN ADDISON'S ANÆMIA.

Lichtheim [13] in 1887 described three cases of "pernicious anæmia" with spinal symptoms. A post-mortem performed on two of them showed degeneration of the posterior columns and to a less extent in the lateral columns. His clinical and pathological observations were soon confirmed by Minnich [15] and Nonne [18]; the latter author before long came to the conclusion that his original idea that the degeneration of the spinal cord was secondary to the anæmia must be incorrect and that both conditions were the result of some chronic intoxication.

In the last twenty-five years spinal cord symptoms have been recognized in Addison's anæmia with increasing frequency as they have become more systematically looked for. In 1902 McCrae [14] found them in 25 per cent. of forty cases; in 1918 Woltmann [21] 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 the figures obtained by Minnich [15] [16], who discovered degenerative changes in 77 per cent. of the spinal cords of a consecutive series of fatal cases of "pernicious anæmia."

Mitchell Clarke [17] in 1904 concluded from a study of the literature and from his own cases that the changes in the nervous system in Addison's anæmia could be clearly distinguished from subacute combined degeneration of the cord, whether or not the latter was accompanied by anæmia. We agree, however, with the view expressed by Barker [2] in 1919 that no definite line can be drawn between Addison's anæmia accompanied by changes in the spinal cord, and subacute combined degeneration of the cord accompanied by anæmia. The difference is simply one of degree, and depends upon whether a hæmolysin or a neuro-toxin is the more active. If either toxin is at first produced alone, there is more time for it to give rise to marked changes; thus when Addison's anæmia is severe and rapidly fatal, there may be no time for any 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 anæmia. 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 anæmia predominates.

III.—NATURE OF THE ANÆMIA ASSOCIATED WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

In some of the nine cases described by Risien Russell, Batten and Collier [20] in 1900 no anæmia was present throughout the disease; in others it developed towards the end, whilst in others it was an "obtrusive symptom from the first and preceded the manifestation of nervous symptoms by many months." They definitely state that repeated examinations of the blood "failed to reveal the alterations found in pernicious anæmia," the changes being those characteristic of secondary anæmia. The red corpuscles were generally normal in shape, nucleated cells were only found in one case in very small numbers, and no megaloblasts or microblasts were present.

In 1904, Mitchell Clarke [17] from a study of five cases of spinal cord degeneration in anæmia concluded that it is by "no means only, nor even most often, that the form of anæmia is pernicious anæmia."

In an article on subacute combined degeneration of the spinal cord published in 1910, Collier [10] states that "severe secondary anæmia" is almost invariably present at some period of the disease, though its development is sometimes deferred till the last stages. But though he

regarded the anæmia as "definitely secondary," his description of the blood corresponds more closely to that of Addison's anæmia. "The colour index is usually above normal . . . Anisocytosis, poikilocytosis, and polychromatophilia are common. Normoblasts are sometimes numerous." He adds, however, that "megaloblasts have not been found, and the reaction for free iron in the liver has not been obtained in any case," but he makes the important observation that the skin not infrequently assumes a striking lemon-yellow colour.

In the same year Byrom Bramwell [7] described a case in which the nervous symptoms developed three years before the anæmia was obvious, but the blood finally presented all the typical features of Addison's anæmia. Post-mortem excess of iron was present in the liver, and there was a great increase in the red bone marrow; the spinal cord changes were typical of subacute combined degeneration. In 1915 [8] he brought forward further evidence pointing to the anæmia being of the Addisonian variety in subacute combined degeneration of the cord, even when it did not first conform to type. He quotes a case in which rapid changes occurred in the blood during the last fortnight of life, the colour index slowly rising in consecutive investigations from 0·8 to 2·3.

Single cases of subacute combined degeneration of the cord have been described by Taylor and Waterman (1903), Collins (1904), Loudon (1913), and Redwood (1920), and two cases each by Grinker (1908), and Hassin (1917), in which the anæmia was definitely of the Addisonian type. Cadwalader, describing nine cases in 1916, stated his belief that subacute combined degeneration was not associated with any form of anæmia except "pernicious" anæmia.

In his latest article on the subject, published in 1921, Collier [11] came to conclusions entirely different from those in his earlier writings. He states that a careful investigation of the blood changes at various stages of the disease and of the post-mortem findings in a large series of cases, has proved beyond any possible doubt that the blood-changes in every case are identical with those that are met with in the various stages of pernicious anæmia, and that a typical post-mortem picture of pernicious anæmia occurs frequently enough in subacute combined degeneration. In contradiction to his earlier papers he says that "megaloblasts may be found in numbers."

Addison's anæmia, particularly in the early stages and during the periods of remission, may present a blood-picture far removed from what is considered to be typical of the disease. This has been recorded fre-

quently and is the experience of all clinicians. A recent case of undoubted Addison's anæmia, in which numerous blood examinations were made and the diagnosis was confirmed post mortem, illustrates this point clearly (Table I).

TABLE I.—VARIATIONS IN COLOUR-INDEX IN A TYPICAL CASE OF ADDISON'S ANÆMIA.

Date	Red blood corpuscles per c.mm.		Hæmoglobin percentage		Colour index
22.9.21	..	2,200,000	..	30	0.7
8.10.21	..	1,500,000	..	20	0.6
1.11.21	..	2,800,000	..	40	0.7
11.11.21	..	2,400,000	..	48	1.2
18.11.21	..	2,088,000	..	58	1.4
5.12.21	..	3,100,000	..	62	1.0
20.1.22	..	1,600,000	..	40	1.25
10.4.22	..	2,400,000	..	40	0.8
15.5.22	..	2,240,000	..	60	1.3
12.6.22	..	1,640,000	..	46	1.4
26.6.22	..	2,440,000	..	50	1.0

TABLE II.—BLOOD EXAMINATIONS IN EIGHT CASES OF SUBACUTE COMBINED DEGENERATION OF THE CORD.

Name	Age	Date	Red cells per c.mm.	Hæmo- globin per- centage	Colour index	Poikilo- cytosis	Aniso- cytosis	Normo- blasts	Megalo- blasts	Leuco- cytes per c.mm.	Wassermann reaction
John B. ..	62	12.7.20	2,650,000	66	1.2	+	+	—	—	3,750	Negative
Wm. B. ..	72	—2.22	2,710,000	48	0.88	+	?	—	—	7,000	Negative
		27.6.22	3,200,000	85	1.3	+	+	+	—	5,090	
Thos. M. ..	65	2.3.22	3,500,000	68	0.97	+	+	—	—	9,500	Negative
		27.4.22	4,580,000	68	0.6						
		29.5.22	4,700,000	62	0.65						
		26.7.22	6,150,000	86	0.7						
Edith J. ..	40	30.3.22	3,300,000	58	0.88	—	+	—	—	7,100	Positive (C.S.F. negative)
J. E. W. (male)	52	14.7.19	2,300,000	52	1.1	++	++	+	+		Negative
		29.7.19	1,500,000	54	1.8	++	++	+	+	2,800	
		16.9.19	3,200,000	94	1.5	?	?	+	+		
		3.3.21	3,400,000	70	1.0	+	+	+	+	6,000	
		—3.21	3,140,000	83	1.3	+	+	—	—	3,700	
Margaret H.	64	—2.22	2,860,000	85	1.5	+	+	—	—	?	Negative
Harriet G.	51	—7.22	4,710,000	56	0.6	+	+	—	—	5,800	Negative
Marion H.	42	—7.22	2,380,000	56	1.2	+	+	—	—	7,920	Negative

It would thus appear probable that many of the cases of subacute combined degeneration recorded, including the nine published by Risien

Russell, Batten and Collier in 1900, in which the blood-picture was not characteristic of Addison's anæmia, were none the less associated with Addison's anæmia. The lemon-yellow colour, which Collier observed in many cases before he came to the conclusion that the anæmia was of the "pernicious" type, is quite characteristic of the latter, and, being caused by staining of the subcutaneous fat with pigment derived from hæmoglobin, it affords just as good evidence of hæmolysis 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 anæmia, is sometimes absent in cases of subacute combined degeneration, because the blood destruction has not been sufficiently severe and prolonged.

During the time our present series of eight cases of subacute combined degeneration of the cord was under observation the blood-picture was not typical of Addison's anæmia, but it was quite compatible with an early stage of that condition, and in those cases in which repeated examinations were made the colour index was at times over one, and the film at times showed the characteristic features (Table II).

IV.—DIGESTIVE SYMPTOMS PRECEDING AND ACCOMPANYING THE NERVOUS SYMPTOMS OF SUBACUTE COMBINED DEGENERATION OF THE CORD.

In 1908 Grinker [12] drew attention to the occasional association of digestive symptoms with subacute combined degeneration of the cord and laid special stress on the frequency of diarrhœa. In 1910 Collier [10] stated that he had occasionally observed symptoms of gastro-enteritis and colitis in the disease. In the same year Farquhar Buzzard [9] stated that gastro-intestinal disturbances may precede or accompany the earliest signs of the nervous disease. In his latest contribution to the subject in 1921, Collier says that in a considerable number of cases symptoms pointing to gastro-intestinal infection, such as vomiting, diarrhœa, anorexia or constipation, were prominent before the onset of nervous symptoms.

In seven of our eight cases digestive symptoms were present. Two patients had had attacks of diarrhœa shortly before the first nervous symptoms appeared; one of these had been actually admitted into hospital on this account. In another case "bilious attacks" with occasional vomiting and attacks of flatulent dyspepsia preceded the nervous symptoms, and in a fourth there was a long history of slight

flatulent dyspepsia. In three others the digestive symptoms only appeared after the first signs of nervous disease.

The digestive symptoms, which are so frequently associated with subacute combined degeneration of the cord, are all symptoms which are often caused by achlorhydria apart from this nervous disease and apart from Addison's anæmia, and which are generally controlled without difficulty by the administration of dilute hydrochloric acid. As these symptoms frequently precede the development of the nervous manifestations, just as similar digestive symptoms frequently precede the development of Addison's anæmia, it seems probable that the achlorhydria precedes the development of the nervous symptoms. It is certainly not due to the anæmia, as the degree of this is generally slight, quite apart from the fact that it is exceedingly doubtful whether anæmia ever does give rise to achlorhydria. The fact that digestive symptoms do not always precede the development of nervous symptoms does not make it any the less likely that achlorhydria always precedes them, as the latter condition may be present for years without giving rise to the slightest indigestion, and it is indeed present in about four per cent. of normal young men without digestive symptoms.

V.—ACHLORHYDRIA IN SUBACUTE COMBINED DEGENERATION OF THE CORD.

We have had the opportunity of investigating eight cases of typical subacute combined degeneration of the cord by the fractional method of gastric analysis. In all of the eight free hydrochloric acid was completely absent throughout the period of digestion. The test was repeated in three of the cases with the same result.

So far as we know no other cases have been investigated in this way. Llewellys Barker [2] found complete achlorhydria in two cases, presumably after an ordinary one-hour test-meal. In one the anæmia at the time of the examination was said to be "quite definitely not pernicious," though the colour index was 1.1, and in the other the red corpuscles numbered 4,000,000 per cm., the hæmoglobin percentage being 90. Barker's observation is valuable confirmation of our results, but the fact that achlorhydria persists throughout digestion is of course of greater significance than the absence of free hydrochloric acid from the contents of the stomach removed in the ordinary way one hour after the meal has been taken. 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.

For purposes of control gastric analyses were made 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 III).

TABLE III.—RELATIVE FREQUENCY OF ACHLORHYDRIA IN VARIOUS CONDITIONS.

	Number of cases	Achlorhydria		Low acidity	"Normal" acidity	High acidity
		Number	Percentage			
Normal (Bennett and Ryle) [5]	100	4	4	1	87	8
Various medical diseases (Bell) [3]	425	63	14.8	53 (12.5 per cent.)	205 (48.3 per cent.)	104 (24.4 per cent.)
Addison's (pernicious) anæmia	66	64	96	1	1	0
Carcinoma of stomach	10	3	33	3	3	0
Subacute combined degeneration of cord	8	8	100	0	0	0
Tabes dorsalis	9	1	11	1	5	2
Disseminated sclerosis	8	0	0	1	7	0

Gastric analysis may therefore give information of real help in diagnosis, the presence of free hydrochloric acid in any fraction of a test-meal being probably a decisive point against the diagnosis of subacute combined degeneration, whereas the discovery of achlorhydria would considerably strengthen 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. These cases are analogous with two others, the only cases in Guy's Hospital in which a diagnosis of Addison's anæmia had been made in spite of the fact that free hydrochloric acid was present in the stomach. At the post-mortem no evidence of hæmolysis was present, one being found to have infective endocarditis, and the

other, who died of lobar pneumonia, having microscopical changes in the spleen, which were typical of Hodgkin's disease.

VI.—ORAL SEPSIS.

The importance of oral sepsis in Addison's anæmia has been almost universally acknowledged since Hunter first drew attention to the subject over twenty years ago. In his article on subacute combined degeneration of the cord, published in 1910, Collier states that septic gingivitis and stomatitis are common in the disease. One of our eight patients had had all his teeth taken out on account of severe pyorrhœa shortly before we saw him. Two others had had all removed twenty or more years earlier because they were becoming loose. The remaining five had more or less severe gingivitis with pyorrhœa and septic stumps. Only one patient complained of soreness of the tongue; it was abnormally red and corrugated, but there was no ulceration. In another the tongue was abnormally smooth and shiny, the papillæ having atrophied to a great extent, although the patient, who was edentulous, was unaware that she had ever had glossitis.

VII.—THE EVIDENCE OF INTESTINAL INFECTION IN SUBACUTE COMBINED DEGENERATION OF THE CORD AND ADDISON'S ANÆMIA.

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 anæmia and in subacute combined degeneration of the cord. In four normal individuals and in eight cases of infective jaundice from Gallipoli investigated by one of us (A. F. H.) with C. J. Martin in Lemnos in the autumn of 1915 no streptococci were present. Among fourteen patients suffering from various medical conditions the duodenal contents contained the *S. longus* in only three instances, one being in a patient with diabetes and slight pyorrhœa alveolaris, and the other two men with cholecystitis, one of whom also had a severe infection of his tonsils; in all three cases the gastric secretion was normal. In four of the fourteen cases achlorhydria was present, together with very severe oral sepsis in two and slight pyorrhœa in a third, but in spite of this no streptococci were found. In every one of the seven cases of Addison's anæmia and the four cases of subacute combined degeneration of the cord which we have investigated

the *S. longus* was found on microscopic examination and was obtained on cultivation of the duodenal contents. (Table IV.)

TABLE IV.—*Streptococcus longus* IN THE DUODENAL CONTENTS.

	Number of cases	<i>S. longus</i> present	Percentage
Normal	4	0	11.5
Infective jaundice	8	0	
Various medical cases	14	3	
Addison's anæmia	7	7	100
Subacute combined degeneration of the cord	4	4	

In spite of the somewhat smaller number of cases, the contrast between the 11.5 per cent. of controls, in which streptococci were found, with 100 per cent. of subacute combined degeneration of the cord and Addison's anæmia, is so striking that the conclusion can probably be drawn that an infection of the intestine with a *S. 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 one of our patients 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 the hands and feet each time it was injected.

VIII.—DISEASES OTHER THAN ADDISON'S ANÆMIA WHICH MAY BE ASSOCIATED WITH SUBACUTE COMBINED DEGENERATION.

Schultze, Nonne and Geitlin are said to have reported cases of subacute combined degeneration of the cord, in which the blood picture was that of lymphatic leukæmia, and Collier refers to a similar case observed by Greenfield. I only know of two cases of lymphatic leukæmia in which a fractional test meal has been carried out. In one of these complete achlorhydria was present, but in the other the curve was normal. It is obvious that no conclusions can be drawn from the two cases, but the presence of achlorhydria in one of them would suggest that in leukæmia the oral sepsis and achlorhydria, which are the necessary conditions for the development of Addison's anæmia and subacute combined degeneration of the cord, may be present. This would explain the occurrence of cases of so-called "leukanæmia," in which the blood picture is a combination of leukæmia and Addison's anæmia, as well as those rare cases of subacute combined degeneration of the cord with leukæmia which have just been mentioned.

It is also said that severe cachexia may be associated with similar changes in the spinal cord, but we have been able to find no detailed description of such cases, the majority of which appear to have been

due to cancer of the stomach. In 30 per cent. of our cases of gastric cancer complete achlorhydria was found with the fractional test meal, and oral sepsis is of course not uncommon. Severe anæmia is more common in cancer of the stomach than in cancer elsewhere. This may be due to the fact that a hæmolytic toxin is sometimes produced when achlorhydria is present and causes a more severe anæmia than would result from the cancer toxins alone. At the same time neuro-toxins might well be produced.

Lastly, subacute combined degeneration of the cord is said to occur in connection with Addison's disease, although here again we have been unable to find any detailed reports. We have, however, had under observation a man suffering from typical Addison's disease with an extreme degree of pigmentation, a very low blood pressure, general asthenia and vomiting, in whom signs of posterior and lateral cord degeneration were present. Further investigation showed that the Addison's disease was associated with the blood changes of Addison's (pernicious) anæmia, so that the nervous changes can be regarded as a complication of the latter rather than of the suprarenal disease.

IX.—SUBACUTE COMBINED DEGENERATION OF THE CORD WITHOUT ANÆMIA.

It has generally been stated that cases of subacute combined degeneration of the cord occur without any anæmia. 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's case, in which anæmia 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 anæmia. It would, however, not be surprising if in a small proportion of cases no anæmia occurred at all, because there is no reason why in some cases neuro-toxins might not be produced without hæmolysins, just as the latter are certainly produced in a considerable number of cases without the former.

X.—PATHOGENESIS.

In their classical account of subacute combined degeneration of the spinal cord published in 1900, Risien Russell, Batten and Collier [20] came to the conclusion that the disease is caused by some toxic agent, which is also the cause of the anæmia, with which it is generally

associated, and that it is not secondary to the anæmia. Writing ten years later, Buzzard [9] suggested that this toxin has its origin in the alimentary canal, and in 1921 Collier [11] concluded that the toxic agent responsible both for the nervous degeneration and the anæmia is of gastro-intestinal origin.

We have already given our reasons for believing that achlorhydria is an essential predisposing cause of Addison's anæmia. Our observations lead us to agree with Collier's most recent conclusion that the anæmia with which subacute combined degeneration of the cord is almost always associated is the so-called "pernicious" form, first described by Addison. It is therefore not surprising that achlorhydria appears to be present as constantly in cases in which subacute combined degeneration of the cord is the earlier and more prominent symptom, as in those in which anæmia is present alone or in which the nervous symptoms remain comparatively unimportant.

Gastric juice has two functions: it helps in the digestion of proteins, and the antiseptic action of its acid helps to protect the intestines from infection with swallowed organisms. In achlorhydria proteins pass into the duodenum in an unaltered form, and bacteria from the mouth and nasopharynx are likely to reach the intestine in far greater numbers than under normal conditions. If achlorhydria is associated with oral sepsis, secondary infection of the intestines is extremely likely to occur. The investigations of Bennett and Dodds [6] show that pancreatic secretion is also deficient in Addison's anæmia. The digestion of proteins is therefore likely to be even more deficient than in cases in which achlorhydria is present alone. Consequently in Addison's anæmia and in subacute combined degeneration of the cord intestinal infection is likely to be associated with the presence in the intestines of excess of undigested or incompletely digested protein. Under such conditions it is not surprising that toxins are produced by the bacterial destruction of proteins in abnormal quantities in the intestines. It is probable that one of these is specially toxic for the blood and leads to a hæmolytic form of anæmia, 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 hæmolytic toxin and still more rare for the neurotoxin to continue to be produced without the other throughout the course of the illness.

XI.—TREATMENT.

The most important part of the treatment of subacute combined degeneration is to attempt to overcome the intestinal infection and so stop the development of the neurotoxic and hæmolytic poisons. Oral sepsis should be thoroughly dealt with. Every tooth which shows the slightest sign of infection on expert clinical examination should be condemned. An X-ray photograph should always be taken of all the remaining teeth, however healthy they may appear, and the slightest sign 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 should be enucleated, and the nose and nasal sinuses should also be examined and if necessary thoroughly treated.

The achlorhydria should be corrected by the administration of large doses of hydrochloric acid. In most cases we have found that a drachm and a half of dilute hydrochloric acid are required in order to compensate for the deficiency of gastric juice (Charts I and II). The acid should be added in the proportion of a drachm to 4 oz. of water in order to make a beverage, the acidity of which is about the same as that of gastric juice. If lemon juice and sugar are added the drink is quite palatable. It should be drunk during the course of each meal, and a little of it should be left over to sip for half an hour after the meal is completed. 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 probably always remains.

Milk which has been soured with an active lactic acid bacillus should also be given for an indefinite period. Most patients can take half a pint three times a day without difficulty.

Lastly, a vaccine should be made from any streptococcus which can be isolated from the sockets of extracted teeth, from the duodenal contents withdrawn through an Einhorn tube, from the fæces and from the urine. This should be given in carefully graduated doses, beginning with very little, and slowly increasing, but it is desirable that no general reaction should follow the injections.

Unfortunately the degeneration of the spinal cord, when it has once occurred, is permanent, so that all that can be expected from adequate treatment of the intestinal infection is that the progress of the disease may be arrested. A certain amount of improvement may, however, result from a systematic course of exercises of the type that Frenkel introduced for tabetic ataxy. On the other hand, if the production of hæmolytic toxins is arrested, the blood shows spontaneous improve-

ment, and recovery can also be accelerated in severe cases by one or more transfusions of blood. Arsenic may be given, but care is necessary, as in the presence of subacute combined degeneration it is difficult to recognize the earliest symptoms of arsenical neuritis.

CHART I.—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 $\frac{3}{4}$ dilute HCl (B.P.) in $\frac{3}{4}$ water (=0.3 % HCl) taken with the gruel and also sipped for an hour afterwards; C, with addition of $\frac{3}{8}$ dilute HCl in $\frac{3}{4}$ of water—normal curve; D, with addition of $\frac{3}{8}$ dilute HCl in $\frac{3}{4}$ water—hyperchlorhydria curve. The shaded area represents the limits for free HCl of 80 % of normal people.

CHART II.—Fractional test-meals to show free HCl in a woman with subacute combined degeneration of the spinal cord. A, without addition of HCl—complete achlorhydria; B, with addition of $\frac{3}{8}$ dilute HCl in $\frac{3}{4}$ water.

Insufficient time has elapsed to be able to report the final result of treatment on these lines. So far it has been most promising. The anaemia, being recognized at an early stage, rapidly improves; in the two cases of [our series which have been [longest under observation it has

actually disappeared, and in one of these the red corpuscles now number over 5,000,000 per cubic millimetre. There has been no increase in the nervous symptoms or physical signs, and in one of the two cases just referred to the tingling of the feet and hands has almost disappeared, and the ataxic and spastic gait has greatly improved, but the physical signs are unaltered.

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