from the residue of the broth filtrate titred 1 in 5,000 and 1 in 500. An autolysate from an agar culture not previously manipulated in any way gave an agglutination titre of 1 in 7,000. We have concluded from these results that autolysates and aggressins are antigenic, not because of the lysis of the bacteria or of the extraction of the antigen by shaking and long standing, but because they contained some of the antigen which had been washed from the exterior of the bacterial cell and which had lost some of its antigenic properties as a result of the method of treatment. The more of the antigen that is previously washed off the cell, the lower will be the titre of the serum stimulated by the sediment left by lysis or the autolysate from the sediment, whether washed or unwashed.

Nitrogen determinations of these bacterial washings show that the total nitrogen in them is very much lower than in that of any other bacterial antigens at present in use, including such well known antigens as bacterial vaccines, glycerinated vaccines, detoxicated vaccines, and serobacterins. The fact that the washings were low in nitrogen content and high in antigenic properties led to experiments to determine, if possible, if washings rendered protein-free would show any immunizing properties. Three methods of precipitating the protein were followed, including the use of acetone, phospho-tungstic acid, and uranium acetate. In the first method the acetone was removed by evaporation under vacuum in order to use as little heat as possible, and in the third method the solution was freed from uranium by precipitation with sodium phosphate. Agar washings of *B. typhosus*, *B. coli*, pneumococcus, streptococcus, and gonococcus apparently protein-free were found to stimulate antibodies of appreciable value, as shown by agglutination and complement fixation tests.

As a final experimental procedure tests were carried out on animals in order to compare these washings with therapeutic antigens prepared after various other methods. The results in every instance were favourable to the washings. In carrying out these tests rabbits were given three intravenous injections each of the antigens, diluted to contain the same number of micro-organisms per cubic centimetre, or their equivalent in antigen, and bleedings were made seven days after the last injection. The serums from these rabbits were then tested for antibody content, according to several well known serological methods, and the results tabulated. As stated above, the antigenic properties of the washings per cubic centimetre, estimated on a quantitative basis, exceeded those of any of the other antigens tested.

It was concluded, therefore, as a result of these last tests and others previously carried out, that these washings more nearly approached the ideal antigen than any which had come under the observation of the writers. This last statement is based on the fact that these washings are in aqueous solution, are low in protein content, are high in antigenic properties, and are practically non-toxic.

CLINICAL RESULTS AND DOSAGE.

Following the experimental work on these "immunogens" steps were next taken to test them on a practical basis. They were sent to a considerable number of clinicians, choosing those who had suitable cases in their clinics, and who were known to be conversant with, and able to give time and attention to, systemic observations of their patients throughout the treatment. While the first trials were carried out more or less as a preliminary measure in order to determine the safety of the remedies, the results justified the procedure, and a more extensive trial was then attempted. The subcutaneous, intravenous, and intramuscular routes for injection of the antigen were compared. So also were various intervals of time in the course of different disease processes. Altogether these trials have been pursued over a period of two years. The intramuscular route appears to be the one of election, and daily injections appear to give the best results. These conclusions are, however, only tentative, since the experience of different observers varies, and the best mode and the interval of injection doubtless depend upon the type of the disease, whether acute or chronic, general or local.

It has been found by a series of trials that the most useful concentration of the antigen is one which allows of

an initial dose of 0.5 c.cm., with increments rising to 2 c.cm., and, on occasion, to 5 c.cm.

It is as yet too early to speak of the main results of the use of this antigen, still less of statistical results. To quote concrete cases, however successful they appear to have been, can avail little, although it is hoped to do this later when a larger number have been collected. Already, it may be said, however, this form of antigen has become the favourite one in the hands of a good many practitioners who have had experience of various types of these remedies. Promising reports are forthcoming in connexion with streptococcal, pneumococcal, and gonococcal infections especially. That reactions of an undesirable kind are absent after injection of this antigen is a fact recorded by almost all those who have used it, and this clinical observation confirms the results of its experimental use in the laboratory.

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SYMPTOMS, PATHOGENY, DIAGNOSIS, AND TREATMENT OF ADDISONIAN ANAEMIA.*

BY

A. T. TODD, M.B., M.R.C.P.,

ASSISTANT PHYSICIAN, BRISTOL ROYAL INFIRMARY; DEMONSTRATOR
OF PATHOLOGY, UNIVERSITY OF BRISTOL.

THIS disease is worthy of consideration on account of its frequency—I have been meeting with one case a month for the last two years—and because of the mistaken diagnoses which have been made: neurasthenia, neuritis, chronic rheumatism, pelvic pressure neuritis, food poisoning, colitis, and carcinoma of the liver have been some of the diagnoses in this series—tragic mistakes, for the disease appears to be amenable to treatment if only the diagnosis is made early.

SYMPTOMS.

Symptoms are often few and vague, and in a series the presenting symptom shows much variability; tiredness or weakness and the symptoms of anaemia are the most common. Dyspepsia is often met with, but pain is usually slight and vomiting rare. Diarrhoea alternating with periods of constipation is a symptom of importance, and is found in about 50 per cent.; it precedes the anaemia by years, and, as the patient has always had it, information about it is not volunteered. It is severe at times and diagnosed as colitis; in one case a severe attack following a meal of suspected fish led me to diagnose food poisoning for two weeks. Premature greyness occurs in a large number of the cases. Glossitis, another symptom which precedes the anaemia, is common; painful cracks and fissures occur for years, and each patch heals slowly, leaving behind it atrophied epithelium devoid of papillae. These atrophic patches spread gradually over a large part of the tongue, and produce the smooth glazed tongue of the declared condition. This glossitis appears to be the sequel of suppurative periodontitis, past or present, and it is found apart from the disease under discussion, though rarely to the same degree. In the less marked cases the glossitis may be unmasked by swabbing the tongue over with dilute acetic acid.

Nervous symptoms, usually those of subacute combined degeneration, are frequent in the later stages of the disease, but symptoms of this condition were the presenting complaints in a third of the series. Abnormal sensations, due to degeneration of the sensory tracts or nerves, are the first and are very misleading, for there is no loss except of deep sensation; the vibration sense, fortunately one of the easiest to test, is one of the first to disappear. As the sensory changes are modified qualitatively, rather than

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quantitatively, a diagnosis of neurasthenia is given. The motor tracts are affected later; the pyramidal tract is, as a rule, the first to suffer; the spastic paresis resulting augments the fatigue of the anaemia. A flaccid paresis usually follows, but Babinski's sign persists. Symptoms due to intoxication of the higher levels are not infrequent, but, apart from those due to the relative anaemia, they occur at a much later stage, and are of no value for diagnosis; acute confusion, depression, and Korsakow's psychosis are frequent. Nervous changes in the upper extremity are less prominent, but of the same kind as in the legs; they occur later. A rapid ascension of the nervous symptoms is occasionally seen; in Case W. it was interesting, although humiliating, to follow the extension to abdomen, thorax, and arms. Trophic changes are late, and, as a rule, terminal.

COURSE.

The disease is of long duration, and has been present for years before it is diagnosed. As will be shown later, it may be termed a congenital disease in most cases. It consists of gradually lengthening waves of anaemia separated by gradually shortening remissions of relatively good health, apart from diarrhoea and glossitis. Hunter says it is the third wave which is diagnosed, but there are probably many ripples, and the waves are difficult to map out. These early waves readily respond to treatment, but recovery occurs without treatment, unless the resistance of the patient is so slight that the condition becomes aplastic at the outset. The later waves are progressively less amenable to treatment, and the aim of this paper is to encourage earlier recognition of the disease.

ETIOLOGY.

This is obscure still. A few cases follow intoxication with known substances—thorium, radium, and x rays; some aniline and arsenical derivatives, and toxins of roundworms and tapeworms. These act by depressing the bone marrow, and cause an anaemia which is indistinguishable from the primary one.

Experimentally an anaemia very nearly related to Addison's type can be produced by injecting known haemolytic substances.¹ Seyderhelm² produced an anaemia of this type in dogs by making a stenosis of the ileum; he found that anaemia developed only when the gut above the stenosis became infected with faecal organisms. This experiment was planned to reproduce the condition found present in cases of Addison's anaemia; it has been known for some time, from operation and *post-mortem* experience, that there is a faecal condition of the contents of the small intestine in these cases, and an atrophic gastro-enteritis similar to the atrophic glossitis already noted.

This infection of the upper alimentary tract would appear to be due to the gastric achlorhydria found in all but a few cases of this disease—the Guy's Hospital school say that it is invariably present; I shall return to this point. The gastric hydrochloric acid is a strong antiseptic—an acidity of pH 4.0 will kill many strains of *B. coli* and streptococci; acidities much stronger than this are found in the normal stomach; I have found acidities of pH 1.0. Culture of normal gastric and upper small intestinal contents shows that most of the bacteria visible are dead, but from these viscera in Addison's anaemia rich cultures of streptococci and other organisms are obtained. It is thought that this failure of normal antiseptics and the absence of a related antiseptic power of the succus duodenalis³ lead to a progressive infection of the alimentary tract with absorption of toxic substances which cause the

anaemia. The cases of anaemia of this type occurring after gastrectomy support this contention.

The cause of the achlorhydria is not yet determined; it is often ascribed to the purulent periodontitis present in practically every case, or previously existing. It is thought that the continuous swallowing of pus leads to gastritis and diminution of acid secretion, just as frequent ingestion of alcohol is known to do. The effect of pyorrhoea on the gastric secretion deserves more study; it is often stated that pyorrhoea leads to hyperacidity, or acid retention, but in several advanced cases I have found complete achlorhydria; this may, however, have been congenital. It has been found that 4 per cent. of normal persons have complete achlorhydria, but Addison's anaemia does not attain this frequency.

Many single organisms have been blamed for the disease: streptococci, spirochaetes, *B. coli*, monilia, and, of late, *B. welchii*. The occurrence of the last-named organism in excess is probably dependent upon the absence of anti-

sepsis. Most importance is attached to streptococci in England and to *B. coli* on the Continent. The toxins of both cause anaemia in animals, and *B. coli* is known to produce a neurotoxin which may well be the cause of the nervous changes so frequently present. Though the common strains of *B. coli* are not capable of producing haemolysins, they do produce haemolytic substances from certain amino-acids which may occur in the small intestine.⁴ Moreover, truly haemolytic strains of *B. coli* would appear to be more frequently found in this disease than is at present generally believed; in five out of six cases

haemolytic strains were isolated at the first attempt; experiments with these organisms are proceeding, and one throws some light on the etiology.

Two rabbits were used and two others kept as controls. Both pairs were put on a vitamin-deficient diet with casein and as much alkali added as the animals would tolerate; this was done to diminish gastric acidity, to supply amino-acids, and to allow bacterial proliferation. The controls were not treated in any other way, but the experimental animals received living cultures of *B. coli* and streptococci isolated from cases of anaemia with nervous changes. Both groups showed anaemia, but the controls rather less. The corpuscles of the controls diminished in size, but the corpuscles of the experimental pair showed an increase (Chart 1). One of the experimental rabbits developed spastic paralysis of the hind legs and was killed; the spinal cord showed patchy degeneration of the white matter, a condition very similar to that found in Addison's anaemia in man. It may be that this change was due to the avitaminosis, but no similar change has been found in the controls, which had exactly the same diet. In addition, the liver of this rabbit showed a free iron reaction, and before death the urobilin in the urine was increased to one hundred times the normal.

The belief that the soil is of as great importance as the seed deserves some notice, especially as several very different seeds are known to be causal. If we replace this gardening simile by another, we have one which satisfies the known facts better: we should liken the patient to a loaded gun—several things may pull the trigger. Hurst⁵ has collected from the literature and his practice 49 cases of familial occurrence of this disease. In one of the early cases of my series there was a strong family history—the patient's mother and grandfather had died of the disease. Having diagnosed Addison's anaemia in this patient (W.) I advised that the relatives should be examined; I found that both her children were anaemic, and that one had complete achlorhydria, and also that one of the patient's sisters was in the early stages of the disease. Since then I have examined the relatives of every case possible, and show the results of eight families in Table I. In the family B.1 the father of the patient died of the disease, and both his children show complete achlorhydria. In case C.1 a brother is

CHART 1.

TABLE I.—*Relatives of Cases of Addisonian Anaemia.*

Case.	Age.	Average Size (μ).	Variation.	Free HCl	Red Blood Cells.	Haemoglobin.
				(N/10).	C.cm. Millions.	Per cent.
Sister of W. ...	42	7.9*	4-10	0	5.0	85
Sister of W. ...	41	7.6	5-10	40	5.6	86
Son of W. ...	19	7.9*	4-10	0	4.6	85
Daughter of W. ...	21	7.8*	5-10	5	4.4	70
Son of Y. ...	30	7.5	5-10	55	4.8	82
Grandson of Y. ...	7	7.5	5-10	34	5.4	?
Daughter of F. ...	21	7.4	6-10	14	4.9	102
Son of F. ...	17	7.4	5-10	16	5.6	108
Son of F. ...	...	7.3	5-10	25	5.3	104
Son of E.1. ...	8	7.5	5-9	0	4.8	78
Daughter of H. ...	30	7.7	4-9	12	4.5	67
Daughter of B. ...	14	7.5	4-10	0	5.7	117
Daughter of B.1. ...	17	7.8*	5-10	0	6.0	112
Daughter of B.1. ...	12	7.5	5-10	0	5.0	120
Daughter of D. ...	25	7.3	5-11	0	4.8	80
Daughter of D. ...	26	7.4	5-10	16	5.7	120

* Suspiciously high values.

suffering from anaemia of long duration, but I have not been able to obtain any further details. Other local familial occurrences are reported to me by Dr. Harvey and Dr. G. Hadfield. A glance at Table I shows that achlorhydria or hypochlorhydria is frequent, and that either anaemia or an excess of red blood corpuscles and haemoglobin is very common. This excess rather points to the presence of some toxic action on the bone marrow with excessive blood formation. Thus hypochlorhydria or achlorhydria and instability of blood formation are very frequent in predisposed subjects, and it is contended that similar conditions are probably present in all cases—that is, that the soil is of importance.

We must leave the etiology, concluding that the toxins or toxic decomposition products of organisms normally saprophytic produce depression of haematopoiesis in a predisposed individual. These toxic substances may act in several different ways: (1) Simple depression of the marrow with the production of badly formed red cells which are rapidly removed from the circulation by the reticulo-endothelial system. (2) The toxic substances stimulate the reticulo-endothelial system to excessive haemolysis, and the marrow is exhausted secondarily. (3) The toxic substances depress the inhibition of the adrenal gland on the reticulo-endothelial system.^{9 11}

We must leave the question at this point, for the evidence does not warrant a definite answer.

CLINICAL SIGNS.

It is rather unfortunate that the disease is called an anaemia, for, apart from the waves of haemolysis, there is little if any anaemia. In the intervals the blood values are normal or above normal. Thus Case W. was investigated by many consultants and two senior pathologists, and was reported free from any sign of anaemia, yet she was very anaemic when I saw her first, and died within three months.

As is well known, during the anaemic periods there is a high colour index, polychromia, and the presence of nucleated red cells, megaloblasts especially being significant. The high colour index requires explanation; in the remissions it is about normal. It appears to be due to the fact, first stressed by Price-Jones,^{6 10} that the average size of the red cells is increased in Addison's anaemia—it is a megalocytic as well as a haemolytic anaemia. This does not mean merely that megalocytes are present, for they are

found in any anaemia; it is the average size, which is greater than normal.

Normally the red cells vary between 5 and 9 μ , the average being given as 7.5 μ . Price-Jones finds it to be 7.3 μ ; my own value and that of some others⁷ is 7.4 μ . Normal values I find to range between 6.9 and 7.6 μ . Table II shows the averages in as wide a collection of blood diseases as I could find, and it will be seen that the values are all below 7.7 μ ; in Table III the values in Addison's anaemia are given, and the lowest is 7.7 μ . In no other disease have such high values been found with the exception of emphysema¹⁰ and malaria, in a case of which I have found a value of 7.8 μ , probably due to the abundance of parasites present. This increase of size is the one constant symptom; it remains during remissions and allows a diagnosis to be made when there is no anaemia. Also, these large cells can contain more haemoglobin, for in the anaemic waves the marrow appears to be able to turn out haemoglobin more easily than corpuscles.

It is probable that this increased diameter of the red cells is not always present, although the exceptions must be very few; two cases of subacute combined degeneration have been described recently which had normal values⁷; in two of my cases the values, though above the normal, were low for Addison's anaemia, and one of these cases was exceptional in showing some gastric hydrochloric acid.

To support a diagnosis of Addison's anaemia we expect to find (1) anaemia, (2) leucopenia, (3) absence of wasting, (4) increase of the average size of red cells, (5) glossitis or its sequelae, (6) achlorhydria, and (7) evidence of excessive haemolysis—that is, excessive urobilinuria and increase of indirect bilirubin in the blood. To every one of these there are exceptions: (1) has already been noted; (2) waves of leucocytosis are not infrequent; (3) wasting is common in the later stages, and when not obvious is often masked by a slight anasarca; (4) exceptions have been noted already,

TABLE II.—*Diseases other than Addisonian Anaemia.*

Case.	Average Size (μ).	Variation.	Free HCl.
Haemorrhage ...	7.3	4.5-9	—
Ditto ...	7.2	3.7-9.5	—
Menopause ...	7.4	4.5-10	—
Ditto ...	7.4	5.2-9.6	0
Syphilis ...	7.3	4.5-9.6	—
Tubercle ...	7.5	5.2-10	—
Ditto ...	6.9	5.2-9	—
Plumbism ...	7.4	4.5-9	—
Xerostomia with glossitis ...	7.1	5.2-9	—
Chronic septic endocarditis ...	7.5	5.2-10	—
Ascaris ...	7.5	6.0-9	—
Gastric carcinoma ...	7.2	4.5-9	0
Sprue ...	7.6	5.2-9.6	—
Osteo-arthritis ...	7.6	5.2-9.6	—
Ditto ...	7.4	4.5-9.6	—
Polycythaemia ...	7.5	4.5-9.6	—
Ditto ...	7.5	4.5-9	—
Lymphatic leukaemia ...	7.5	4.5-11	—
Ditto ...	7.1	5.2-12	—
Ditto ...	7.5	5.2-11	—
Von Jaksch's anaemia ...	7.0	3.7-12	—
Purpura ...	7.2	5.2-9.6	—
Ditto ...	7.5	5.2-9.6	—
Acute rheumatism ...	7.3	4.2-9	0
Post partum ...	7.4	5.2-9	0
Spleno-medullary leukaemia ...	7.5	4.5-9	—
Lymphogranuloma ...	7.6	5.2-10	—
Secondary (?) ...	7.5	4.2-9.6	0

TABLE III.—Addisonian Anaemia.

Case.	Average Size (μ).	Variation.	Subacute Combined Degeneration.	Result.
Y.	9.1-9.12	5.2-12	—	Alive.
F.	8.4	3.7-13	Present	?
X.	8.36	4.5-10.8	—	?
Y.1	7.95	4.5-11	Present	?
Z.	8.4	5.2-10.5	Present	?
As.H.3	7.9	4.5-10.5	—	?
N.	7.85	4.5-9.8	Present	Alive.
M.	7.8	5.2-9.6	Present	Alive.
W.1	7.7	4.5-10.5	Present	Alive.
W.	9.3-8.2-7.9	3.7-12	Present	Dead.
E.1	7.9	4.5-12	—	Alive.
W.2	7.8	3.7-10.6	—	Alive.
A.	8.0	?	—	Alive.
J.	8.7	4.8-12	Present	Alive.
C.	7.9 7.8	3.0-11	Present	Dead.
C.1	7.9-7.7	4.5-11.2	Present	Dead.
E.	8.4-7.8-8.4	3.7-12	—	Dead.
F.1	8.0	3.7-11.2	Present	Dead.
J.1	7.8	4.5-10.6	—	Alive.
S.	8.0	3.7-12	—	Alive.
B.	7.95	4.5-12	Present	Alive.
B.1	8.4	3.7-13	Present	Alive.
B.2	7.8	3.7-12.6	Present	Alive.
D.	8.2	4.5-13	Present	Alive.
D.2	7.82	4.5-9.6	Present	Alive.

if we are to conclude, in agreement with the Guy's Hospital school, that subacute combined degeneration occurring in anaemia is confined to the Addisonian type—a conclusion not generally accepted; (5) glossitis may be little marked; (6) in a series of 51 cases Faber and Gram⁸ found 4 in which some free hydrochloric acid was present; my Case M. also shows free hydrochloric acid; these appear to be the only cases which have been fully examined; it has been objected that the cases of Faber and Gram were bothri-cephalus anaemia; this cause was not found, although these observers were alive to the possibility; in my case there is no evidence and little likelihood of worm infection; (7) evidence of excessive haemolysis is not found in the remissions and in the cases becoming aplastic (note Chart 2 of Case W.—the urobilin and bilirubin diminish to normal values in spite of increasing anaemia).

Measurement of the red cells may be made in several ways; the best, I think, is actual measurement with a carefully calibrated ocular micrometer. A green monochromatic screen is of help. Three to five hundred cells, taken as they come, are measured and an average made, or a curve, as recommended by Price-Jones,⁶ is compared with the normal. Where there is considerable increase a glance is sufficient to give a diagnosis, but in the lower values fully 500 cells should be measured. Such a count takes me about ninety minutes. American observers find that 200 cells are sufficient, and that the count can be made in twenty minutes.⁷ There are several ways other than this. A very pretty one, when the staining turns out well, is to make the suspect film on the top of a film from a diabetic patient with acidosis; the corpuscles of the latter take a basic dye, while the suspect's cells take an acid stain.¹³ In the lower values this method is of no value.

The cause of this megalocytosis is not the achlorhydria, for a glance at Table II will show that in several cases with achlorhydria normal values are found; in bothri-cephalus anaemia, where there may be no achlorhydria, the values are above the normal.⁸ The experiments of others¹ and my own show that this permanent increase is to be ascribed to the presence of toxic substances acting on the marrow; a temporary increase occurs in some forms of acidosis.¹²

APLASTIC ANAEMIA.

This is most commonly regarded as a separate disease, although usually discussed with Addison's anaemia. The diagnosis is not made frequently, and is apt to be considered a guess. The features of this anaemia are said to be: severe anaemia; presence of a haemorrhagic tendency due to thrombopenia; absence of evidence of blood regeneration, marked leucopenia and scarcity of nucleated red cells; smallness in size of the red corpuscles; absence of marked or any excess of haemolysis; presence of a gelatinous marrow in the long bones; generally fatal issue, the few survivals probably being cases of purpura haemorrhagica, which simulates, and may even terminate in, aplastic anaemia.

Four cases in my series have acquired these features after showing all the signs of florid Addisonian anaemia. In Case W., shown in Chart 2, the red cells diminished in size and number and at the same time urobilin and bilirubin fell to normal values. The explanation is that the marrow is turning out so few corpuscles that there is not enough material for excessive haemolysis. In Case E. (see Table III) the low diameter coincided with a severe wave of anaemia; the following higher value accompanied a remission. In Cases C.1 and C.2 a diminishing value is seen; these cases could not be worked out so completely as Case W.

CHART 2.—Note that urobilin index is the product of percentage and amount in ounces.

From these observations, confirmed by *post-mortem* examination in Case C.2, it is inferred that aplastic anaemia is merely a terminal phase of Addison's type, and that this variety would be more frequent if the patients survived longer. It may, however, be the first manifestation of this or any other anaemia where there has been a heavy intoxication of the marrow or where the haematopoietic power is low at the outset. It is important to recognize the transition, for treatment is disappointing in this stage; blood transfusion leads to transient amelioration only; in two of the cases it gave me the impression that it accelerated death.

Before considering treatment the part played by the endocrine glands requires mention. Evidence of disease is often found *post mortem*, and this would be expected. Thyroid changes are common⁹; Case Y. requires 3 to 5 grains, and Case D. has been receiving 15 grains of thyroid extract daily; the possible influence of the adrenal gland has been noted. It will be of interest if both the diseases named after Addison are found to be associated with lesions of the same gland. The condition of the pancreas is of greater practical importance, for evidence of defect in its external secretion is found with some frequency, and this would have been regarded as inevitable until recently; the external secretion of the pancreas was said to be stimulated by secretin produced by the inter-

action of hydrochloric acid and the duodenal mucosa. According to this theory the digestion of proteins was almost impossible in achlorhydria, for peptic and tryptic digestion could not occur. We now know that hydrochloric acid is not indispensable, but the atrophic condition of the duodenal mucosa raises the suspicion that it is deficient of pro-secrelin. Examination of the stools shows that in many of these cases flesh is poorly, if at all, digested; yet, in view of the anaemia, the patients are urged to eat as much of it as possible; the result is putrefaction and the production of further toxins to depress the marrow.

TREATMENT.

There are many treatments, and the effect of any one is difficult to gauge when the nature of the disease is remembered; no matter what treatment is given, the marrow will respond as long as it can, and a remission will follow. At the present stage of our knowledge the indications are:

1. Stimulation of the blood-forming activity of the marrow.
2. Improvement of gastric and intestinal digestion.
3. Diminution of intestinal infection.

Stimulation of Haematopoiesis.

Septic foci around the teeth, accessory sinuses, or wherever found, should be removed. The removal of tissue causing haemolysis—that is, splenectomy—used to be practised with some frequency, and is still advised. It is not performed so frequently as it was, and should only be considered where there is splenomegaly. The series of Giffin and Szlapka¹⁴ is regarded as the chief authority, and these authors base their conclusions on survival. A review of the operation in other places gives a high mortality, and shows that the remissions were not often of long duration; survival is very variable with any treatment; my Case Y. has survived eleven years, although for about eight of them he had no treatment. Another operative method in use at present is the removal of marrow from the long bones, with the hope that a new marrow will regenerate; it is usually preceded by blood transfusion, and remissions occur.

More direct methods are the exhibition of arsenic, which remains our sheet anchor; it may be given in any form, and the form does not appear to be very important. In certain schools in Germany it is given in enormous doses. If there is actively spreading nervous disease arsenic must be carefully watched, for it is a nerve poison. Iron does not appear to be of any value, but it is hoped that its use intravenously may cause a blockade of the reticulo-endothelial system and give the same result as splenectomy, without its danger; experiments on this line are being made. Cholesterolin, with the object of providing stroma for the red cells, has been recommended; I have not had any success with it.

Blood transfusion, an excellent stimulus for the bone marrow, is widely practised, and if the marrow is still capable of response it acts well. In the cases showing signs of aplasticity it does little, and may well be conceived to do harm; when the marrow is almost exhausted the provision of donor's blood may remove any stimulus to regenerate, and the struggle is given up. It has been noted that in two such cases transfusion gave the impression that death was hastened. When blood transfusion is given it is advised to group the donor and recipient and give blood of the same group; if the blood count of the patient is under one million grouping is difficult, and a Group IV. donor should be chosen. The results of transfusion are well known, and many, some even permanent, remissions follow; it should be pointed out that at the menopause an anaemia occurs associated with some excess of haemolysis, and in about 50 per cent. with achlorhydria; these cases do well on iron and arsenic, but transfusion gives a permanent remission. With earlier recognition of Addison's anaemia transfusion will be seldom required.

Improvement of Digestion.

This is largely accomplished by the provision of the missing hydrochloric acid. This must be given in large

doses, commencing with 45 minims and increasing as rapidly as possible to at least 2 drachms. The dose must be modified to the diet; this latter dose after a meal like afternoon tea will give pain. The 2 drachms of acid are given in 7 to 10 ounces of water flavoured with sugar and lemon juice; this is sipped towards the end of, and shortly after, each meal. It must be taken for the rest of the patient's life. This amount of acid has been found to bring the acidity of the stomach to the normal, and should permit peptic digestion, and it is hoped that it will stimulate pancreatic secretion. Where there is active dyspepsia this should be preceded by a short course of bismuth and hydrocyanic acid until gastric irritability is less marked. If, as is common, pancreatic digestion is defective, flesh should be sparingly ordered at first; the diet should be mainly lacto-vegetarian. In several of these cases I have tried pancreatic extract, but have not found any certain benefit.

Intestinal Antisepsis.

In addition to the help afforded by the procedures noted in the section above there are some more direct methods. Koumiss, lactic cultures, or *B. acidophilus* cultures all have the same action and are interchangeable; they act, like the lacto-vegetarian diet, by increasing the acidity of the intestinal contents, and so reduce the growth of streptococci and *B. coli*. As a lacto-vegetarian diet is monotonous and sometimes repugnant, this method of giving cultures with an ordinary diet will afford a welcome interlude. Given with a mainly carbohydrate diet they are of more value still.

Kaolin, from its power of adsorbing toxic substances and precipitating micro-organisms, is indicated. It is given either dry or suspended in water the first thing in the morning; my patients readily increase to three heaped teaspoonfuls.

Colonic lavage through an artificial anus appears to be giving good results, and is a rational treatment where the urinary indican remains high in spite of the measures so far outlined.

Vaccine therapy (streptococci and *B. coli*) is still on trial; it is too early to be sure of its value.

Treatment of the nervous symptoms is the same as that of the anaemia. When the anaemia has disappeared the only treatment is re-education, but this gives very good, although slow, results.

CONCLUSIONS.

1. Addison's anaemia is a common disease, and through most of its course is not an anaemia.
2. Diagnosis is possible in the pre-anaemic stage.
3. In the early stages treatment is highly successful, but must be perpetual.
4. In the later stages exhaustion of the marrow, or aplasticity, supervenes, when treatment is without result.
5. Hereditary transmission of the anaemia, and of relative or complete achlorhydria, is so frequent that the relations of any case should be examined for these defects.

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