REMARKS ON THE NATURE AND TREATMENT OF PERNICIOUS ANÆMIA.

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(Concluded from page 1029.)

SUCH seem to me to be the causes and explanations of the symptoms and pathological changes found in "pernicious anæmia." To recapitulate somewhat: the patients are first subjected to varied debilitating conditions, which produce at first an anæmia differing in no respect from so-called "simple anæmia" or from "chlorotic anæmia." In a small number of persons degenerative changes occur in the blood vessels, which lead to persistent capillary hæmorrhages; the manufacture of red blood corpuscles and hæmoglobin does not keep pace with the loss, and the persons ultimately die from anæmia, or the process may be stopped and they recover. Some cases develop almost entirely from chronic external blood losses, the internal hæmorrhages playing but a small part in their causation.

Why so small a proportion of individuals out of the millions subjected to these debilitating influences develop the degenerative vascular changes is difficult to explain except by analogy with such conditions as mental derangement or phthisis. Out of the enormous numbers of human beings who have undergone severe nervous strain, losses, or disappointments, comparatively few succumb to insanity; we are all more or less exposed to tuberculous infection, and yet only a certain percentage become affected. We explain this by heredity and many other complex considerations, and the reasons why only a few anæmic persons should develop pathological vascular changes are just as obscure.

As has been previously pointed out, the causes of the initial anæmia are still imperfectly known, and cases sometimes occur in people who are apparently healthy and living under good conditions. Hunter may be correct in holding that a cadaveric poison breaks down the blood in some cases, and if this be so, debilitating conditions with hæmorrhages need not necessarily precede the "pernicious anæmia." It is possible too that degenerative changes in the small vessels may occur spontaneously in certain people. In these also there might be no preceding causes or illnesses of a marked kind, and few *post-mortem* lesions would be observable except in the light of our very recently acquired knowledge. But conclusive evidence is wanting on all these points. As I have previously pointed out, the capillary hæmorrhages found *post mortem* may be very few in number, and this might lead us to adopt Hunter's view that in some cases, at least, a blood-destroying body may be the cause of the condition, but the course and history of such cases lead me to believe that hæmorrhages have been more frequent previously and have become absorbed.

TREATMENT.

The prognosis is grave, and treatment is generally regarded somewhat hopelessly—rather too hopelessly. It is very difficult to obtain statistics as to cure, but Quincke records 7 recoveries out of 21 cases, Müller only 3 out of 44, while Pye-Smith has collected 20 cases of recovery compared to 110 deaths. Dr. Hale White insists that a large number of so-called recoveries in hospital practice drift out of sight, and ultimately relapse and die, but although this may be true to a certain extent, yet it is certain that many cases have made permanent recoveries.

Cases secondary to malignant disease or atrophy of the stomach must at once be recognised as hopeless, but, on the other hand, the most brilliant results have attended the treatment of those due to intestinal parasites. Out of 72 cases of tapeworm anæmia Schauman records only 12 deaths, 4 of which patients were practically moribund when first seen, and the other 8 very far gone; Runeberg¹ says that before the discovery of the causal connection between the parasite and the "pernicious anæmia" all his cases died in spite of treatment

with iron, arsenic, tonics, and good diet, whereas afterwards out of 19 treated with anthelmintics only 1 proved fatal. Reyharr² records 13 cases without a death. After the parasite is expelled the patient has to be kept in bed on light diet, with tonics and iron, so as to assist recovery from the extreme debility, but the blood begins to improve at once, and in six to eight weeks the patient is practically well. The febrile attacks commonly persist for one or two weeks, or longer.

In ankylostomiasis recovery takes place also when the parasites are expelled. In Germany, Austria, and Italy, where the habits and surroundings of the patient are fairly good, deaths are now almost unknown; but in Fiji, in coolies (dirt eaters, and living on very poor food), Hirsch reports 26 deaths out of 126 cases.

We may now consider the ordinary run of cases which are seen in this country. It is to be regretted that a special name like "pernicious anæmia" has been given, as if it were a distinct disease, to the extreme blood changes which sometimes result from atrophy of the stomach, cancer, and other diseases which are necessarily fatal, while the same blood changes may also result from conditions not in their nature incurable. The application of a special name leads us to classify all cases presenting these blood changes in the same category, and tends to a neglect of the etiological factor in diagnosis and treatment. The frequent unsuccessful results of treatment are, partly at least, attributable to the very general idea that the condition is a specific disease always of the same nature, and to be cured, if cured at all, by certain somewhat empirically used remedies.

Therapeutic measures are not so often without result as is generally assumed, for which we have the authority of Habershon, who says, after very considerable experience, that many patients at an early stage recover completely under bracing air, good diet, and iron. One great hindrance to successful treatment in curable cases is encountered in the very advanced state of anæmia and debility in which patients often first apply for advice. The gastric and intestinal glands are already in a state of fatty degeneration, and this gives rise to severe gastric dyspepsia with frequent and obstinate attacks of diarrhoea. In fact diarrhoea very commonly exhausts the patient and brings the case to a fatal termination. If one saw many of these cases earlier there can be little doubt that the results of treatment would be much more favourable. Probably when the vascular degeneration has become very pronounced it is difficult to restore the capillaries to their pristine condition, and the internal bleedings still persist. Ignorance of the original exhausting cause, which is therefore allowed to go on, must also no doubt be sometimes held blamable for failure.

In my experience the cases in which most may be hoped from treatment are those which have been brought on by external hæmorrhage, but even in these, time, patience, and very great care are needed. Two cases which I have under observation at present illustrate this. In one it has required four months to raise the corpuscles from 1,900,000 to 3,170,000 per c.mm., and the hæmoglobin from 20 to 50 per cent. She had bleeding piles for three years, and a year ago lost a great deal of blood at her confinement, which precipitated matters. In the other a year has been required to raise the corpuscles from 3 to 3½ millions, and the hæmoglobin from 30 to 52 per cent. The second patient had also suffered for many years from bleeding piles, she was of a deep yellow tint, and for the first three months of treatment lay in bed in a state of almost complete debility and apathy, and without making the slightest progress towards recovery, or improvement in her blood condition. She has since gradually improved, has lost her yellow tint, and is able to do household work without extreme fatigue. In both of these cases there was dyspepsia, and in the second frequent diarrhoea. The first was treated exclusively with gastric sedatives and careful dieting along with small doses of iron which had frequently to be intermitted. The second had in addition comparatively large doses of iron and arsenic. In such cases any blood loss should be stopped with the most jealous care. Piles should be specially treated and if necessary removed, while if menstruation occur (as it occasionally does) the patient should be instructed to at once stop it with a hot douche.

Sandoz³ relates a case due to excessive fermentation in the

stomach and intestine, which he cured by persistent lavage; while Jürgensen⁴ states that a patient of his recovered after the expulsion of enormous numbers of Bacterium termo from the bowel. Hunter has advocated strict intestinal antiseptics, and it is possible that in some cases this may prove effective. Habershon⁵ describes a case where very severe vomiting and dyspepsia were the only symptoms besides the "idiopathic anæmia," and recovery took place in five months under treatment with bismuth, diet, and iron. There seems therefore to be a considerable number of cases due to gastro-intestinal derangements, in which recovery occurs under strict attention to diet, local sedative measures, and antiseptics.

When the condition has been brought on by hardships and poor feeding, as seems to occur much more commonly on the Continent than here, good feeding will no doubt arrest it if the patient be not too far gone. In pregnancy and lactation a similar timely interference to avert the initial anæmia is indicated.

Bleeding ulcers in the bowel sometimes give rise to chronic fatal anæmia. Several cases have been reported, and the possibility of this with its bearing on treatment may be borne in mind. Blood is seldom seen in the fæces, but hæmin will be present. In the only case of severe anæmia which I have met with due to chronic small bleedings from the bowel, I was able to obtain both hæmoglobin and hæmin, showing that the source of the blood must have been low down the intestinal canal, and that the blood was not digested. The man recovered.

Lastly, Müller has suggested that in cases where constitutional syphilis is present, antisyphilitic treatment may do good. His results are not very encouraging, however, as out of four cases only one recovered. Laache has also reported a case of recovery, but the treatment was very mixed.

SPECIAL REMEDIAL AGENTS.

Iron.—It has been stated and reiterated by nearly all writers that iron is of no value in pernicious anæmia. This is to a limited extent true, in so far that iron fails to cure or improve many patients, but such a way of stating the case is hardly correct. If a case is curable at all (excluding those which are necessarily fatal) then iron is bound to be of value, as it is of value wherever a deficiency of hæmoglobin has to be made good. The iron of the hæmoglobin must be obtained from somewhere, and if a patient once begins to pick up, and the number of red corpuscles to increase, the iron in the liver and elsewhere will soon be used up, and the metal has to be supplied by the food, reinforced by a further supply in the usual pharmaceutical forms. The reason why iron so often fails to cure the anæmia is simply that, owing to the numerous hæmorrhages, blood manufacture does not keep pace with the blood loss. For the same reason iron is apparently quite useless in the anæmia of scurvy or purpura so long as the bleedings continue.

Quinke treated his seven cases of recovery with iron, and Wilks⁶ and Finlay⁷ both record cases in which arsenic failed to effect any improvement, and iron was afterwards successful.

It is always advisable, therefore, to give iron. It is often, however, very badly borne by the stomach, and has frequently to be cautiously given in small doses of non-irritating preparations. Often it agrees well enough in large doses. Non-irritating preparations (ferrum tartaratum, ferri et ammonii citras) may be given *per rectum*, and act efficaciously enough if iron cannot be taken by the mouth.

Arsenic and Phosphorus.—Arsenic was first strongly recommended in anæmic conditions by Isnard (1865), but its value in pernicious anæmia was first drawn attention to by Dr. Bramwell. Since then it has been largely used, and a number of cases of recovery from "pernicious anæmia" have been recorded after its administration. Broadbent found phosphorus valuable in two cases, and Gowers⁸ in two cases of lymphadenoma with anæmia found it to increase the number of corpuscles. On the other hand phosphorus has frequently proved ineffective (Bradbury, Eichhorst, and others), and it has never attained the reputation of arsenic. The mode of action of both is little understood, but neither of them can replace iron in the blood corpuscles, and hence as they both have a powerfully stimulant and alterative effect on bone, it is probably not far from correct to assume

that they may stimulate the bone-marrow, and thus increase the number of blood corpuscles produced by it. We have no definite knowledge on this point however.

Arsenic has undoubtedly started many cases towards recovery by increasing the number of red corpuscles, but it cannot supply their most necessary constituent, and hence after the increase has begun it seems advisable to use iron to help in maintaining the improvement. Too often it seems to simply stimulate the exhausted bone marrow into a last display of activity, and the temporary improvement is followed by a relapse and death. Many cases of this temporary improvement have been recorded (Pye-Smith, Barrs,⁹ and others). Fürbringer¹⁰ states that of 57 cases treated by himself with arsenic, 27 died, 16 had improved, and 10 remained *in statu quo*—not a very brilliant record.

It is probable that at the present time too much reliance is placed on arsenic, it has come to be looked upon as a specific in "pernicious anæmia," acting in some mysterious recondite way, and is used in a routine fashion to the exclusion of therapeutic measures based, so far as possible, on etiological considerations. Of its good effect in some cases there can, however, be no reasonable doubt.

Transfusion.—I have had little experience of transfusion; 3 to 6 ounces of defibrinated blood seems to have been the amount generally used by others. Frequently it produces some slight temporary improvement, in a very few cases permanent benefit has followed, and in many it is reported to have caused considerable systemic disturbance with albuminuria and hæmaturia. Some authors have recorded a fatal issue almost immediately after. Theoretically, if one wishes to give blood, it seems to me that frequently repeated subcutaneous injections of defibrinated human blood (as used by von Ziemssen¹¹ and Silbermann¹²) would be the most efficacious and least dangerous method of administration, but a sufficient supply would be difficult to obtain. One cannot use the blood of animals, as, whether given by a vein or subcutaneously, it tends to cause dangerous systemic disturbance to a much greater extent than human blood.

I think that both experience and theory are on the whole against transfusion of blood in chronic anæmia. If it be given under the idea of supplying iron in the form of hæmoglobin, it is a cumbersome and bulky way of giving a very small quantity, with some risk of sepsis and other dangerous complications. The serum is in this case a useless addition. If it be given under the idea of supplying red corpuscles the number is again very small, and at best they only survive for a few weeks or less. In this case, however, it may help to tide over threatened death from anæmia, and give time for other measures to be carried out. I have heard the opinion expressed that the serum may act as an antitoxin, antagonising a supposititious toxin which is destroying the blood corpuscles, but hitherto no evidence has been advanced which supports this view.

Bone Marrow.—Professor T. R. Fraser¹³ has reported a case of pernicious anæmia treated with 3 ounces of ox and calf bone marrow daily. Iron, and subsequently arsenic and salol, were also given, but under these no improvement took place until the bone-marrow was administered in addition. Dr. A. G. Barrs¹⁴ has also published a case in which arsenic had failed to effect any improvement, and in which he then administered bone marrow without any other drug. Complete recovery took place in about two months.

Owing to the kindness of Dr. John Wyllie, I have had the opportunity of studying the effects of bone-marrow in a case under his care in the Royal Infirmary. The patient was a woman, aged 41, with a history of some degree of menorrhagia and a very doubtful history of melæna, but the cause of the extreme anæmia was never satisfactorily determined. On admission the corpuscles numbered 1,400,000 per c.mm., and the hæmoglobin was 20 per cent. of the normal. Under treatment with iron and arsenic these improved to 1,700,000, and 30 per cent., but she then ceased to progress. Bone-marrow, 1½ ounce daily, was given without any other treatment except careful dieting, and in eighteen days the corpuscles had fallen to 1,200,000, and the hæmoglobin to 15 per cent. The bone-marrow disagreed with her stomach, owing to its being so fat, and a larger quantity could not be borne. She died afterwards, but an examination was not obtained.

It is difficult to account for the good results obtained by Drs. Fraser and Barra, if recovery were really due to the bone-marrow, and not to the other treatment. I have examined the marrow as supplied in the Royal Infirmary and in the Leeds Infirmary, and found it to consist of yellow marrow which is not a hæmopoietic tissue like red bone-marrow, but is entirely fat with a little connective tissue. The amount of iron present in it was also determined in three specimens from different animals, with the following results: 26 g. contained 0.001 g. Fe; 20 g. contained slightly under this amount; and 100 g. contained 0.0025 g. Fe. That is to say, 1 ounce of bone marrow contains about $\frac{1}{4}$ grain of iron or less. I have also examined the amount of iron present in red bone-marrow from the calf; 40 g. contained only 0.0035 Fe, while 26 g. contained 0.002 Fe, equal only to about $\frac{1}{8}$ gr. of iron per ounce. The butchers informed me that a calf only yields about 3 or 4 ounces of such marrow, and that a large supply would be very difficult to obtain. Clearly it cannot be the iron which is beneficial, if benefit does result.

CONCLUSIONS.

1. That "pernicious anæmia" is not a special disease,
2. But is secondary to numerous exhausting conditions.
3. That these induce an initial anæmia
4. Which is followed in certain cases by degenerative changes in the blood vessels.
5. That capillary hæmorrhages result, and induce an excessive degree of anæmia.
6. Some cases are due chiefly to external bleeding.
7. That these bleedings account for all the characteristic symptoms and *post-mortem* appearances.
8. That treatment should be based on etiological considerations.

The clinical work on which this paper is based was done in Chalmers' Hospital almost entirely, and I am extremely indebted to Dr. George W. Balfour, who, during the five years he was physician to the hospital, most kindly placed at my disposal as many beds as I had anæmic patients to put into them. A good deal of experimental and pathological work was done in the Laboratory of the Royal College of Physicians of Edinburgh, and I am indebted to the Superintendent, Dr. Noel Paton, for several valuable suggestions. I am also under great obligations to my friends Dr. Gulland, Dr. Gibson, Professor of Chemistry in the Heriot-Watt College, and Dr. Dobbin, of the Chemical Department of the University of Edinburgh, for the very great amount of trouble they have taken in checking all my pathological and chemical observations.

REFERENCES.

- ¹ *Deut. Archiv f. Klin. Med.*, xli, 304, 1887. ² *Deut. Archiv f. Klin. Med.*, xxxix, 31, 1886. ³ *Correspondenzbl. f. Schweiz. Aerzte*, 1887. ⁴ *Verhandl. des Congress. f. innere Med.*, 1887, 97. ⁵ *Lancet*, 1863, i. ⁶ *Lancet*, 1885, i, 653. ⁷ *Lancet*, 1885, i, 374. ⁸ *Practitioner*, i, 21, 1878. ⁹ *BRITISH MEDICAL JOURNAL*, 1895, i, 358. ¹⁰ *Verhandl. des XI Congress. f. innere Med.*, 58. ¹¹ *Deut. Archiv f. Klin. Med.*, xxxvi, 169, 1885. ¹² *Deut. med. Wochenschr.*, 1885, 445. ¹³ *BRITISH MEDICAL JOURNAL*, 1894, i, 1172. ¹⁴ *Loc. cit.*

A CASE OF PERNICIOUS ANÆMIA TREATED WITH BONE MARROW.

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SINCE the publication of Professor Fraser's paper on "Bone Marrow in Pernicious Anæmia" in the *BRITISH MEDICAL JOURNAL* for June 2nd, 1894, records of a number of cases of pernicious anæmia and other diseases of the blood in which the same treatment was adopted have appeared from time to time. The therapeutic value of bone marrow cannot, however, be said to have been even yet precisely determined. The following case of pernicious anæmia, which presents some features of special interest, and was under treatment for a protracted period, is recorded as a contribution to the subject.

M. W., a woman, 73 years of age, was admitted to the Argyll and Bute Asylum on May 20th, 1891. Throughout her stay in the asylum she was silly in manner and conversation, and her memory was somewhat impaired. She was subject to periodical outbursts of excitement, during which she devel-

oped delusions of suspicion. The case-book records state that her bodily health was much impaired on admission, but that it subsequently greatly improved.

When I first saw the patient, in April, 1894, she was obviously anæmic, but her appearance was far from suggesting the degree of anæmia which was subsequently found to be present. The skin was slightly yellow in hue, and the subcutaneous fat abundant. The principal symptoms were great weakness and, later, prostration, various pains of indefinite localisation (chiefly in the abdomen), pruritus vulvæ associated with slight cystitis, anorexia, palpitation, and shortness of breath. No retinal hæmorrhages could be discovered, pyrexia was absent, and there was no oedema of the feet. On June 5th the blood was examined, and the red corpuscles were found to be reduced to 700,000. The white corpuscles were about 2,000. A few irregular corpuscles and some megalocytes were present, but no nucleated red corpuscles could be discovered. The corpuscles formed imperfectly into rouleaux. The patient at this time was completely prostrate, and could only take very small quantities of liquid nourishment.

She was ordered finely divided bone marrow in milk. She got at first, perhaps, an ounce a day, but the quantity was increased as soon as possible to two ounces. Improvement took place very rapidly. By June 13th the red corpuscles had risen to 1,140,000, and the patient had gained strength considerably. By July 23rd the red corpuscles had increased to 1,710,000. The patient was now able to sit up in bed, and to take most of the ordinary diet. The marrow was given to her on bread and butter, or minced with bread crumb. She was very particular about her food, and would sometimes surreptitiously give away the marrow to other patients, or conceal it about her bed, partly because she was tired of it, and partly, as she said, because she was tired of life and did not wish to take anything which might make her better. She complained greatly of obscure abdominal pains and of weakness. During August her general condition continued to improve, so that she was able to be up for a short time every day. There was a slight falling off, however, in the number of the hæmocytes, which on August 25th were 1,450,000, while the hæmoglobin was 25 per cent.

The patient was now ordered Bland's pills, three to nine daily. On September 17th the hæmocytes were 1,850,000, the hæmoglobin 25 per cent. Subsequently the hæmocytes fell to 1,500,000. The patient continued to gain strength, her appearance became much more healthy, and she was able to be up nearly all day.

On November 6th she was ordered arsenious acid $\frac{3}{8}$ gr., afterwards increased to $\frac{1}{2}$ gr. (in pill), in addition to the iron and bone marrow. Under this treatment the improvement was still further maintained, and the hæmocytes and hæmoglobin rose steadily. The highest point noted was reached on January 31st, 1895, when the hæmocytes numbered 2,500,000, while the hæmoglobin stood at 39 per cent.

On February 21st the patient died of oedema of the lungs, after having laid up for a few days by a sharp attack of quinsy.

Post mortem both pleuræ were found to be completely adherent. The lungs were congested and extremely oedematous—water-logged, in fact. All the viscera were in a condition of advanced fatty degeneration. No hæmorrhages were anywhere present. Furthermore, sections of the liver stained with ferrocyanide of potassium and hydrochloric acid revealed a copious deposit of iron in the peripheral zones of the lobules. It will be noticed that a number of the usual signs of pernicious anæmia were absent in this case. The percentage of hæmoglobin was uniformly less than the percentage of hæmocytes. The blood—fresh, in normal salt solution tinted with methyl violet, and in films fixed and stained in various ways—was carefully and repeatedly searched for nucleated red corpuscles without a single example being observed. No retinal hæmorrhages could be discovered. Throughout the progress of the case pyrexia was absent (except on two occasions when the patient was suffering from tonsillitis). Dr. Muir informs me that he has seen fatal cases of pernicious anæmia in which the same symptoms were absent.

As the patient had been living under the same conditions