CLINICAL LECTURE ON PROGRESSIVE PERNICIOUS ANÆMIA WITH SPINAL SYMPTOMS.

Delivered in St. Bartholomew's Hospital.

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GENTLEMEN,—The case furnishing the text for this lecture is one of so-called pernicious anæmia which has afforded us much thought recently. It supplies us with many of the typical features of such cases which we have to consider in detail. The whole subject of pernicious anæmia is a large and still a vexed one. Its recognition as a distinct malady is due to Dr. Addison of Guy's Hospital, who first described its peculiar nature some half-century ago, when he also, as he stated, "stumbled upon" the peculiar disease of the adrenal bodies which now bears his name. He termed this disease "idiopathic anæmia," and this is still a synonym of the disorder. Since the period referred to much work has been bestowed on the subject, and much has come to light by means of modern methods of research which were unknown in Addison's days. But, even now, I meet, in the best textbook we possess, with the following statement from a former distinguished pupil of this school, Dr. Rolleston, which may sufficiently indicate to you the difficulties which still invest the study of this disease: "Our ideas," he declares, "of pernicious anæmia are but a mass of shifting hypotheses."

A similar statement might, indeed, have often been made respecting the knowledge of the time concerning various diseases about whose nature we feel certain to-day. It would have rejoiced the heart of Addison to know all that is now ascertained about pernicious anæmia, and who can doubt that ere the next half century is completed its pathogeny and treatment will be fully understood?

Our patient was twice under care in Matthew Ward. His first sojourn lasted two months. The following notes relate to the earlier history:

E. P., aged 36, an engine driver, admitted to Matthew Ward, December 10th, 1898.

History.—He had been ailing from December, 1897, when he began to have attacks of vomiting coming on immediately after food. Later, the attacks of vomiting were accompanied by diarrhoea, lasting about three days. These attacks occurred about once a fortnight. He continued at his work up to December 3rd, 1898, when he had an attack of sickness and diarrhoea worse than usual, followed by a fainting fit. He stated that he had been losing flesh lately and getting paler, and complained of tired and languid feelings. He had had rheumatism ten years earlier, but no other illness. His father was living, aged 84; his mother was dead. He had three healthy brothers and sisters.

Condition on Admission.—He was a thin, sallow-looking man, and very anæmic. The skin had a peculiar yellowish, almost bronzed colour. His manner was languid. The tongue was clean. There was no pigmentation of the buccal mucous membranes, which were rather pale. The pupils were equal and dilated. The temperature was normal. There were no physical signs in the chest. The pulse was 120, and there was a *bruit de diable* in the neck. The abdomen was natural. Pulsation was visible in the middle line; no viscera were felt. There was slight œdema of the shins. The urine, of specific gravity 1020, contained neither albumen nor sugar. Ophthalmoscopic examination revealed nothing abnormal.

December 16th. Blood count:

Red corpuscles, 31.8 per cent., 1,594,000.

White, 4,000.

Hæmoglobin, 36 per cent.

There was a relative eosinophile and coarsely granular leucocytosis. Poikilocytes were present, but there were no nucleated red corpuscles.

December 20th. Some improvement in general condition. Hæmoglobin, 27 per cent.

January 10th. Blood count:

Red corpuscles, 4,100,000.

Hæmoglobin, 42 to 45 per cent.

No poikilocytes.

Improvement maintained, gaining weight.

January 17th. Blood count:

Red corpuscles, 3,400,000.

Hæmoglobin, 55 per cent.

January 31st. Red corpuscles, 4,600,000.

February 8th. Red corpuscles, 4,655,000; hæmoglobin, 53 per cent.

On admission the patient's weight was 98t. 13lbs.; on discharge it was 108t. 6lbs.

The improvement was most marked, and clearly ensued as the result of treatment by rest, good diet, with wine, red bone marrow, and the action of arsenic. The patient resumed his duty after a while, and came to report himself to us at

intervals. He never recovered his original health, having been a vigorous and robust-looking man, and he continued to take the above remedies more or less for about eighteen months. We come now to his second admission to the ward on August 8th, 1900, when Dr. Ormerod took charge of him in my absence. He had followed his occupation till thirteen weeks previously. One day after being wet through he became ill, and had pains in his limbs and loins. He did his duty with much difficulty, feeling very poorly, and finding his knees very weak and painful. He grew pale again. He began to vomit once or twice daily a week before admission, and had occasional shiverings. There was constant sleepiness, and he frequently felt faint. Dyspnoea ensued on any exertion. No hæmorrhage occurred. He walked feebly and said he had done so for some weeks. He had lost his appetite and had pain after food. His condition plainly indicated a relapse of the anæmia and, in addition, the onset of some grave disorder of the spinal cord, as the following notes will show, taken by my house-physician, Dr. Rowland:

He is very anæmic, of a "faded leaf," earthy tint. There is plenty of subcutaneous fat. The conjunctivæ are icteric; the pulse is 108, soft and small; the respirations 20; the temperature 99.6° F. The heart's apex beat was in the third space, half an inch inside the nipple line. The area of cardiac dullness was small, and there was a soft hæmic murmur at the apex. The second sound was not accentuated. The percussion note over the lungs was good, with vesicular breathing; no adventitious sounds. The abdomen was natural; some gaseous distension. No viscera felt. There was no œdema of legs.

August 25th. Blood count:

Red cells, 1,600,000

White cells, 5,000

Hæmoglobin, 27 per cent.

The patient sweated profusely, and was very exhausted and languid. On August 20th the blood count was the same; he got up each evening. There had been steady, uninterrupted improvement in appearance, in strength, and in feelings. There was slight pyrexia for a few days after admission. The temperature only occasionally rose above 99° now.

September 7th. The improvement had not continued. The patient was quite unable to stand, and complained more of his legs, which were increasingly numb. Knee-jerks active, some anaesthesia.

September 14th. Icteric tinge of conjunctivæ has been increasing lately: appetite is better than it was a week ago. The following notes were taken:

Nervous Symptoms.

Subjective.—Feeling of swelling and numbness in both legs (especially left) reaching from feet to groins and over lowest part of spine. Legs feel weak. There is numbness in hands also, most marked in little and ring fingers.

Movement.—There is weakness in all muscles of both legs, no definite paresis. No wasting. Left leg weaker than right; calf circumference equal.

Sensation.—There is complete loss of sense of position, legs can even be crossed without patient's knowledge.

Touch.—There is nearly complete anaesthesia below a line encircling knees below patella, but dipping down popliteal space in loop over calf, in "small sciatic area." Above this sensation is apparently normal, not by any means brisk.

Pain, Heat, and Cold.—No alteration can be found in these sensations.

Reflexes.—Knee-jerks equal, exaggerated, obtained by smiting above patella. No ankle clonus. Plantar reflexes very brisk of extensor type. All skin reflexes in leg seem brisk. Bladder and rectal control is complete. No trophic changes. Arms, some degree of anaesthesia (not worked out), loss of sense of position partial.

September 17th. "All muscles of both upper and lower extremities react normally."

September 22nd. Salol. gr. x given three times daily.

September 27th. Blood count:

Red cells, 1,520,000.

White cells, 4,000.

Hæmoglobin, 26 per cent.

September 19th. Loss of rectal control yesterday for first time.

September 20th. Patient was given gas and four molars extracted.

October 2nd. There has been difficulty in micturition for the last three or six days. A catheter was passed on October 1st and about 3xl drawn off. Only 5ij were passed in the following twenty-four hours, and catheter was again passed to-night to relieve the painful sense of fullness. Many small motions have been passed unconsciously during the three previous days.

The patient was very miserable. The sense of swelling of the legs to twice their normal size continued. The anaesthesia had advanced and was almost complete up to a line half way up the thighs. There was no definite anaesthesia in the arms or hands, but there was a feeling of numbness up to the wrists. He had wandered at night for three or four nights, and had talked a good deal.

October 5th. Blood count:

Red corpuscles, 1,500,000.

Hæmoglobin, 32 per cent.

October 7th. Since catheter had been passed twice daily the patient had felt much more comfortable and had slept well through the night. He was increasingly weak, but not very restless. This day he complained of pain in the lower part of the spine.

October 9th.—The patient complained of severe headache (frontal). He seemed weaker and at times slightly delirious.

October 10th.—He was very much weaker. At 6 A.M. the temperature rose suddenly to 104° F. The respirations were 34 and the pulse 120, at times very small. During the day he very gradually sank and died at

10 P.M. About an hour before death the temperature rose to 105°. The pulse was 136 and of very small volume. One hour after death the temperature was 106.2°.

Necropsy.

Pernicious anæmia. Iron reaction well marked of liver and kidneys. Fatty kidneys. Softening of lumbar portion of spinal cord. Gall stones. Emphysema of lungs (slight).

The post-mortem examination was made on October 11th, fourteen hours after death.

External Appearance.—Well-nourished anæmic body, abundance of cutaneous fat of a rich yellow colour, muscle red.

Head.—Cranial bones natural; no pus in either antrum or in ethmoid cells. Decayed teeth had been removed.

Dura mater and sinuses, arachnoid and pia mater natural.

Arteries natural.

Brain, 48 ounces. *Spinal cord,* softening of about 2 inches of the upper lumbar cord with deliquescence.

Eyes and Ears.—Eyes not examined. No suppurative in either ear.

Chest.—(Esophagus, glands of neck, larynx, and trachea natural.

Lungs.—Right, 20 ounces slightly emphysematous. Left, 19 ounces.

Heart.—Thirteen ounces. Pericardium natural; no obvious fatty degeneration of heart muscle. Valves natural. Aorta and vessels natural.

Abdomen.—Peritoneum natural. Stomach natural; no pyloric thickening.

Intestines.—Solitary follicles conspicuous. No other obvious change in large or small intestines.

Liver.—Sixty-four ounces, pale, perhaps slightly fatty, gives a brilliant blue iron reaction, staining being highly selective and in the outer zone of the lobules. In the gall bladder forty deeply pigmented blackberry-like gall stones.

Spleen.—Seventeen ounces, large, red, and flabby. No iron reaction.

Pancreas, abdominal lymphatics, suprarenals all natural.

Kidneys.—Fourteen ounces. Pale and somewhat fatty. Iron reaction brilliant and highly selective, limited to cortex.

Ureters and bladder and organs of generation natural. Joints not examined.

Right Tibia.—On section uniformly pallid condition of the marrow.

The temperature was not remarkable throughout this relapse. A few days after admission it reached 100.8°, but remained between 98° and 99° for the remainder of life. Two days before death 100.2° was reached, and on the last day it rose to 105°, and continued to rise after death, being 106.2 one hour subsequently.

This case then presented a complete picture of the malady we are considering. The degree of recovery was apparently very satisfactory after the first course of treatment, but, as not infrequently happens, a relapse occurred. Hence, doubts are not unnaturally felt as to the ultimate and complete recovery in any case of this nature. The disease is regarded by some as one whose nature is to amend and relapse, the degree of recovery, or apparent recovery, depending upon the degree of recuperative hæmogenic power in any given case. There thus appears to be a balancing, as has been said, of hæmolytic and hæmogenic processes, the latter usually prevailing in the long run.

We looked in vain during life for any evidence of toxic source, and, although the mouth was not foul, in deference to Dr. Hunter's views, paid attention to the state of the teeth. Several of these being carious were removed, and the mouth was washed out regularly with antiseptics. We also gave salol for a time with the hope of combating toxic influences in the alimentary canal. Quinine, iron, and arsenic were given, and red ox marrow in the diet.

The spinal symptoms were the final manifestations of the disease, and many cases have been recorded which illustrate the varied effects of its toxæmia upon the cord.

In our patient these were gravely indicated by the motor and sensory changes observed in the limbs. The electrical reactions were normal. The cord was found to be much softened in the lumbar region. It has been reserved for further minute examination, which is not yet completed.

The hæmolytic debris was extremely well shown by the iron reaction in the liver and kidneys which you see in these specimens which I hand round, immersed in formalin, and this condition you may regard as pathognomonic of the malady we are considering. The kidneys are apt to become blackened *post mortem* in these cases, as Dr. Garrod pointed out, owing to the decomposition of the iron into sulphide.

The condition of the marrow in one of the tibiae was examined, and it was found, as you see, to be uniformly pale and of a yellow tinge. Dr. Andrewes, our pathologist, tells me that there is as yet insufficient knowledge to justify any decided opinion as to the prevailing condition of the bone marrow in cases of pernicious anæmia. The appearances and intimate elements of it appear to vary much in different cases. They commonly consist of nucleated red corpuscles and giantoblasts.

The condition of the blood was characteristic during life in

respect of poikilocytosis. No nucleated red globules were found. The hæmoglobin was deficient, and there was eosinophilous leucocytosis at first. These conditions improved markedly under treatment but returned with the relapse. No retinal hæmorrhages occurred.

The present conception of this distressing malady regards it as the result of a special form of blood destruction, so-called hæmolysis, occurring in the course of the portal circulation, induced by the action of some toxic matter produced in and absorbed from the alimentary tract. The disease is therefore a chronic infective form of toxæmia, which induces profound anæmia, and it is surmised that this toxin is of bacterial origin.

It cannot, then, be rightly regarded as a primary anæmia, for there may possibly be more than one source for the toxins which induce it. At this point our knowledge is as yet imperfect. There may be other than toxic causes for this malady; atrophy of the stomach, for instance, may sometimes induce it. The evidence for the toxic theory is very strong, and we owe much of the elucidation on the subject to the work of Dr. William Hunter. He has shown that the products of this portal hæmolysis, whereby hæmoglobin is discharged from the red corpuscles, are deposited in the liver, spleen, and kidneys, in the form of pigments composed of iron granules, which are readily detectable by appropriate reagents, or as other varieties eliminated by the kidneys, and known as urobilin and hæmatoporphyrin. Together with this destructive process we find indications in some cases of this malady of efforts to repair the loss by a process of blood renewal or hæmogenesis. These are to be met with especially in the bone marrow, which appears to revert sometimes to its fetal condition. I show you here some bones which have been bisected to show the state of the marrow in different cases of this disease. You see that they vary much in character, some showing very pale or mottled conditions, and others a dark purple aspect. No uniform condition has as yet been observed in respect of these myelitic changes, but they demand careful study in each case. They possibly represent varying degrees of effort on the part of Nature to induce a reparatory hæmogenesis.

In this case we failed to find any overt cause for the malady; but we must take note of the gastro-enteric symptoms, which in this, as in most examples of the disorder, are commonly met with. We can hardly suppose that the carious teeth were to blame for its existence. The disease should surely be a very common one if this condition suffices to originate it, for there are plenty of foul mouths in the world; but in all cases of pernicious anæmia the state of the mouth and the alimentary canal calls for attention in respect of septic infection and appropriate treatment.¹ We must remember that some persons are especially liable to septic infection.

The diagnosis of pernicious anæmia is not difficult. The disease should be suspected in any case of profound anæmia, which comes on in this country insidiously. The possibility of some condition on which the anæmia depends must be considered. I think the disease which most resembles it is cancer of the stomach, certainly in respect of the pallor of the patient, but the extreme wasting and gastric symptoms in the latter are generally prominent. The fat is usually retained in all forms of anæmia, apart from cancer and tuberculosis.

Chlorosis may simulate pernicious anæmia. The age and sex help you here. The condition of the blood is also different, since there is much greater deficiency of hæmoglobin and less diminution of red globules in chlorosis. Poikilocytosis is also rare in the latter. In splenic anæmia the enlarged spleen is a marked feature. There is a form of grave endemic anæmia secondary to the parasitic attacks in the intestines of the ankylostoma or the bothriocephalus. If there is any suspicion of their presence, the fæces must be examined for ova, and these cases may yield to appropriate treatment for the respective parasites.

I have already mentioned the methods of treatment that are to be employed. My experience confirms the benefits already recognised from the use of arsenic and red ox marrow, together with good diet and wine. Dr. Hunter suggests the employment of an antistreptococcus serum, inasmuch as pyogenic organisms appear to be constantly taking part in

the general infection, but we have no experience as yet to indicate whether this may prove beneficial or not. The malady is a terrible one, and demands our best efforts both to learn its exact nature and to find remedies for it. When a measure of improvement is secured by any method, it is proper to continue the treatment for long periods, and not to rest satisfied that the disorder is overcome.

NOTE.

¹ Dr. Hunter, however, makes out a very strong case for his views in regard to infection from the mouth. *Vide Lancet* January 27th, February 3rd and 10th, 1900, for admirable accounts of the disease.

PRESIDENTIAL ADDRESS

ON

THE PRESENT POSITION AND FUTURE WORK
OF THE BRITISH MEDICAL ASSOCIATION.

*Delivered at the Opening of the Session of the North of Ireland
Branch, October 18th, 1900.*

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the Branch.

GENTLEMEN,—My first and most agreeable duty is to return my warmest thanks for the compliment you have paid me. To be President of the largest Branch of the British Medical Association in Ireland is indeed a high honour; and it is in no small degree enhanced by the fact that this is a Society of one's fellow-practitioners in Ulster, some of whom are old college friends, others teaching colleagues, a large number former pupils, whose success in life is particularly gratifying to me; and some, alas! now very few in number, like Dr. Redfern, my most respected teachers. Speaking of Dr. Redfern, may I say it was he who, in years gone by, revolutionised the teaching of anatomy in Ireland; and it was to his unceasing efforts, and dignified and attractive personality, and the great reputation of his two brilliant colleagues, the late Dr. Andrews and Dr. Gordon, that the initial success of the School of Medicine in Belfast was largely due.

THE PROGRESS OF SCIENTIFIC MEDICINE.

In thinking over a suitable subject for a presidential address it is only natural that, at the close of a century, the characteristic note of which has been, as stated by Mr. Balfour in his masterly address to the summer meeting of the Cambridge University Extension students, its fertility "in the products of scientific research to which no other period offers a precedent or a parallel," one should feel the present occasion would be an admirable opportunity to look backwards and try to answer the question, How has the science and art of medicine in its various departments been influenced by all those wonderful discoveries of this century, which dazzle us not merely by their ingenuity and by the rapidity with which they have followed one another, but still more by their practical application, in this most utilitarian age, to the diagnosis, prevention, and treatment of disease? "No century," according to Mr. Balfour, "has seen so great a change in our intellectual appreciation of the world in which we live," and we, from a purely medical point of view, join with him in saying now, "We not only see more but we see differently." Even within the experience of many present to-day, has not the science of bacteriology completely revolutionised our ideas in almost every branch of medicine? And within the last few years a new and most promising field for original investigation has been opened up by the combined clinical and laboratory investigation of the blood; and so, at the end of this century, another medical science arises—hæmo-pathology. Among all the advances of science in this most wonderful period, none to my mind is so extraordinary as that we are now able—thanks to improved methods of investigation and to the invention of instruments of precision—to estimate the total amount of blood in the human body in health or during disease, and its colouring matter, to find out

its specific gravity, its reaction, its coagulability, the presence in it of parasites and bacteria, and to count the number of the red and white corpuscles, and so to make out their numerical relationship to one another; all this being accomplished by the examination of a drop of blood obtained by a slight puncture of the finger or lobe of the ear.

This new method of medical examination is still in its infancy. Queen's College and our Medical School in Belfast are helping in its evolution, and it promises to be of enormous assistance to doctors, no matter in what department their special line of practice may be, in the diagnosis, prognosis, and treatment of disease. Let me cite a few examples showing the practical value of this method of clinical investigation of the blood in disease.

(a) You have all, I am sure, had at times cases of young patients under your care where you were in doubt whether the disease from which they were suffering was typhoid fever or tuberculous meningitis; but now, by the aid of this science of hæmo-pathology, we can, by an examination of a drop of the blood of the patient, arrive much nearer to a certain diagnosis: for in typhoid we have at least as early as the end of the first week Vidal's reaction, a condition not met with in tuberculous meningitis, while in the latter most serious malady there is a marked increase in the numbers of the white corpuscles, leucocytosis as it is now termed, a condition not present in typhoid, where the white corpuscles are normal in number, or even below the normal. Sometimes we meet with obscure cases of fever following childbirth, where, although we may be suspicious that the patients are suffering from septicæmia, still they present clinically a typhoid appearance. To make the diagnosis certain, an examination of the blood will show, if typhoid is the cause, Vidal's reaction and no increase of the leucocytes; if, on the other hand, sepsis is giving rise to the morbid condition, there will be an absence of Vidal's sign but marked leucocytosis.

(b) You may again be in doubt whether an obscure swelling in some part of the body consists of pus, or whether suppuration is occurring in a previously existing tumour. Now, leucocytosis is an important sign of abscess formation. The surgeon, in a case of appendicitis, is able to say that the disease has advanced from the catarrhal to the suppurative stage by the fact that there is a distinct increase in the number of the leucocytes, increasing often from normal (6,000 to 10,000 in a c.mm. of blood) to 15,000 to 40,000.

(c) Further, suppose there is a case of disease of the middle ear. It is of the utmost importance to know early if pus has formed. Now, in simple catarrh of the middle ear, leucocytosis—that is, an increase of white cells beyond 10,000 in a c.mm. of blood—rarely is found, while in suppurative otitis there may be an increase of leucocytes up to 20,000 to 30,000. In suppurative disease the patient's condition, from a prognostic point of view, is more favourable if leucocytosis diminishes, less so if the number of white cells increases.

(d) Not only can leucæmia be diagnosed from such maladies as carcinoma and tuberculosis, but the various forms of anæmia, simple and secondary, chlorosis, and pernicious anæmia, can be distinguished by this clinical investigation of the blood.

(e) In malarial fever—a disease found in so many parts of the British Empire—if a drop of the blood is examined a few hours after the initial shiver, parasites are discovered in the interior of the red corpuscles peculiar to each type of the disease, these being introduced by the bite of particular species of mosquitos, as proved by the experiments conducted in the most pestilential part of the Roman Campagna, near Ostia, at the mouth of the Tiber, and at home by the London School of Tropical Medicine, as well as by the members of the Liverpool Expedition sent to West Africa—a piece of scientific research so creditable to British medicine.

It is curious that in phthisis the coagulability of the blood is diminished, hence calcium chloride is so useful in the treatment of hæmoptysis; in scurvy there is a marked reduction in the alkalinity of the blood (scurvy, according to Professor Wright of Netley being "a condition of acid intoxication"), and so curable by the administration of alkalies, such as acetate, tartrate, citrate, or lactate of soda. By the estimation of the specific gravity of the blood great and rapid changes in the amount of that fluid can be detected, and in this way it has been shown that the thirst so common after abdominal operations is really due to a rapid reduction in the volume of the blood, especially the plasma.

Every doctor who has resided in India is aware how unsatisfactory is our knowledge of the fevers of that country, and the *Lancet* has recently urged (September 12th, 1900) the authorities to provide the necessary apparatus, so that in the principal hospitals, by an examination of the blood, scientific accuracy may be obtained as to the diagnosis of the protean types of fever met with in India. Surely this is a matter of pressing necessity when it is recollected that nearly half of the deaths and invaliding of the British troops in India, and nearly one-third of their total sickness is due to some form of fever. An examination of the blood will settle the diagnosis of malaria and typhoid, and it may afford further information as to the other varieties of fever in India. It is based largely on such examinations of the blood that the question of vaccination against typhoid (enteric fever) rests. This problem—of