A Clinical Lecture ON THE TREATMENT OF PERNICIOUS ANAEMIA.

DELIVERED AT THE ROYAL INFIRMARY, EDINBURGH.

BY

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I BEGAN the study of pernicious anaemia now almost forty years ago, when I was physician to the Newcastle-on-Tyne Infirmary. In the year 1874 two cases of profound anaemia were admitted to the Newcastle Infirmary under my care; both died, as these cases so often do. The disease was then very little known in this country, though it had been described by the celebrated Dr. Addison. He met with a number of cases of fatal and apparently causeless anaemia; he termed it "idiopathic anaemia," and it was while hunting about in the bodies of patients after death to try and find the cause of this peculiar form of anaemia that he discovered the remarkable lesion of the suprarenal capsules which is the pathological substratum of the disease, which we now, of course, all know as Addison's disease.

The terms "pernicious anaemia" and "progressive pernicious anaemia" were subsequently given to the idiopathic anaemia described by Addison, for it was found—as, indeed, he had found—that the patients suffering from this form of anaemia always, or almost always, died, whatever the form of treatment employed. Addison failed to discover any cause for this profound and fatal anaemia, and we are still ignorant of its exact cause.

Now, profound anaemia arising without any loss of blood or other apparent cause may, theoretically at least, be due to one or other of two great causes—namely, either a defective production or an excessive destruction of the red blood corpuscles. Either of these two conditions may, when acting in a marked degree, produce a very profound form of anaemia.

About the time that I commenced the study of pernicious anaemia a celebrated American physician, Dr. Pepper, Professor of Medicine, and afterwards Principal or Provost of the University of Pennsylvania, described the lesion in the marrow of the bones found in the bodies of patients who have died of pernicious anaemia. He termed the disease "myelogenous anaemia," for he thought it was due to defective production of red blood cells in the bone marrow. The bone marrow is, I need not say, the most important red-blood-producing structure. Pepper thought that this lesion in the bone marrow was the fundamental lesion of the disease.

Some years later, when I was assistant physician to this infirmary, I had as one of my assistants Dr. William Hunter, who has identified himself with the subject of pernicious anaemia. While he was my assistant in the out-patient department he made a series of very important observations with regard to the *post-mortem* findings in pernicious anaemia and with regard to the artificial production of anaemia in animals. He came to the conclusion that pernicious anaemia is not due to defective formation of red blood corpuscles in bone marrow, as Pepper had supposed, but to excessive destruction of the red blood cells in the portal circulation. In proof of this he advanced the fact that the liver in pernicious anaemia shows a large excess of iron.

In my early studies of pernicious anaemia I paid particular attention to the condition of the blood. I found that the red blood corpuscles, instead of being biconcave, circular discs, all about the same size, varied greatly in size and shape, some being larger, some smaller than the normal, and many of them misshaped in various ways—poikilocytosis, as it is now termed—some of them apparently nucleated. I described and figured this condition in the *Edinburgh Medical Journal*. The nucleated condition of the red corpuscles, as I took it to be—in unstained films parts of some of the corpuscles are more

deeply pigmented than normal—was subsequently shown to be merely an apparent, not a true nucleation, due to a concentration of the haemoglobin in a particular part of the corpuscles. But we now know that in many cases of pernicious anaemia some of the red blood corpuscles, stained by methylene blue and eosin, are actually nucleated; indeed, this nucleated condition of the red corpuscles is a characteristic feature of the blood in many cases of pernicious anaemia; but it is not the condition I described.

When Dr. Hunter told me of his researches and of his view that pernicious anaemia is due to an excessive destruction of red blood corpuscles in the portal circulation, I asked him how he accounted for the enormous number of small, immature, imperfectly-formed red blood corpuscles which is such a striking feature of the blood in pernicious anaemia—the presence in the blood of so many immature red blood corpuscles seems to show that there is a defective formation of red cells. He met that argument in, I think, a perfectly legitimate and satisfactory way. He said if you destroy at one end of the circulation, say in the portal circulation, an enormous number of red blood cells, you call upon the bone marrow—the red-blood-forming tissue—for an excess effort, with the result that a great number of immature and imperfectly-formed red blood corpuscles are thrown into the circulation. That certainly seems a plausible explanation, but it is not, perhaps, the whole truth.

We may take it, then, that there is excessive destruction of red blood corpuscles in the portal circulation, together with an excessive production of immature and imperfectly-formed red corpuscles in the bone marrow. Free iron is liberated and is stored up in the liver—this is seen *post mortem*. The bone marrow is called upon to produce an excessive quantity of red blood cells, and it is, as we know, found on *post-mortem* examination to be in an abnormal condition. The destruction of the red corpuscles in the portal circulation is probably due to the presence of some toxin, which is probably absorbed from the gastro-intestinal tract. But, if this is so, we do not know what the toxin is.

Now it is possible that the toxin which destroys the red blood corpuscles in the portal circulation also stimulates the bone marrow to excessive formation of red blood corpuscles, or perhaps acts injuriously upon the bone marrow; and, if this be so, the lesion in the bone marrow is not merely a compensatory effort to meet the excessive destruction of red blood cells which is undoubtedly present; it is not merely a secondary lesion, but is, in part at least, a primary lesion.

The bodies of persons who have died from pernicious anaemia are extremely bloodless; the tissues are very often stained yellow—canary or primrose yellow; the most characteristic naked-eye lesion is the fatty condition of the organs, particularly of the heart; the thrush-breasted or faded-leaf appearance of the muscle of the left ventricle is highly characteristic. In many cases small petechial haemorrhages are scattered throughout the body—in the retina, on the surface of the heart, lungs, brain, for example. Professor Stockman of Glasgow suggested some years ago that these haemorrhages are the cause of pernicious anaemia. But that is not so; they are merely secondary—a consequence not a cause of the condition. In some typical cases of pernicious anaemia no petechial or other haemorrhages are found on *post-mortem* examination.

In the fatal cases of pernicious anaemia which I examined *post mortem* in 1874, I was struck by the fatty condition of the heart. I knew that arsenic is a remedy which is often very beneficial in cases of fatty heart, and I said to myself, Why should one not try arsenic in cases of pernicious anaemia? I tried it, with very marked success.

During 1875 six cases of pernicious anaemia were admitted under my care in the Newcastle-on-Tyne Infirmary; all of them were treated with arsenic. One of these early cases lived for thirteen and a half years, and ultimately died of the disease, having had several relapses. That patient lived, I think, longer than any other case which has come under my notice.

It is a very remarkable fact that the first cases which one treats with any new remedy are often singularly successful. My experience of the thyroid treatment of

psoriasis shows this. In the first case of myxoedema which I treated by thyroid I gave too large doses, and produced acute thyroidism; it was attended with profuse desquamation of the skin. I argued that if thyroid tissue—I was then using the raw gland—could produce this extraordinary desquamation in myxoedema, it would probably be of use in psoriasis and other skin diseases. In the first three cases of psoriasis in which I tried it the result was remarkable. The extraordinary success in these first cases led me to think that I had made a remarkable discovery. There is no doubt that it was a discovery and advance, for many cases of psoriasis and certain other skin diseases are very greatly benefited by thyroid treatment, but the remedy is an uncertain one. Some cases of psoriasis are cured by it, or temporarily cured by it; others are not. I have had many successful and many unsuccessful results. I mention this for the purpose of showing how careful one should be in drawing therapeutic or indeed any other conclusions from a limited number of cases. I will give you another example—a remarkable coincidence which shows how fallacious it is to reason from a limited number of cases. Of the first 7 cases of pernicious anaemia which I treated by salvarsan three were women and four were men. The names of all the women began with P, and the names of all the men with S. Now if one limited oneself to these facts, and if one were dealing with a new disease one might perhaps argue that the names of all women affected with pernicious anaemia begin with P, and the names of all men affected with pernicious anaemia begin with S. This, of course, is a bizarre illustration, but it shows what I mean.

Since I began to treat pernicious anaemia with arsenic in 1875 I have had a long and continuous experience of this and other methods in the treatment of this very grave and fatal disease. The result has been to show that cases of pernicious anaemia, if they are first attacks, usually do exceedingly well under arsenical treatment; that many of them get apparently quite well, but that, with very few exceptions, they relapse and ultimately die of the disease. The remedy seems to lose its effect and to be much less efficacious in the relapses than in the primary attacks. Consequently, we want some better remedy than arsenic for pernicious anaemia.

Dr. William Hunter has directed attention to the condition of the mouth and tongue, and emphasized the importance of oral sepsis. I think he has attached far too much importance to this point. I have seen and published several cases of pernicious anaemia in which there were no decayed teeth, and in which for years before the onset of the disease the patient had had no teeth. I have seen several cases in which there had never been any ulcers on the tongue or any inflamed or irritative condition of the buccal mucous membrane; I look upon the ulcers in the mouth merely as part and parcel of the disease, perhaps due to the same toxin which destroys the red blood cells, but not the primary, or even a predisposing, cause of the disease.

In addition to arsenic, a great number of other remedies have, of course, been employed in the treatment of pernicious anaemia. Iron has been given, but in the great majority of cases it does harm rather than good. One would expect this from the condition of the blood in pernicious anaemia.

In the normal male the red blood corpuscles number 5,000,000 per cubic millimetre, the haemoglobin equals 100 per cent. (with Gowers's instrument, which we use, we rarely get 100 per cent.), and the colour index, which represents the percentage of haemoglobin divided by the percentage of red corpuscles, equals 1 ($\frac{C.I. 100}{R.C. 100} = 1$). In pernicious anaemia there is an enormous diminution of the red blood cells; in an average well-marked case the red blood corpuscles number 1,000,000 instead of 5,000,000; the haemoglobin equals 30 per cent. or more; and the colour index is consequently above the normal 1.5 or more ($\frac{C.I. 30}{R.C. 20} = 1.5$). The haemoglobin is in many cases much higher than this; in some cases the colour index is 2 or even more.

In chlorosis, another form of idiopathic anaemia, the red blood corpuscles usually number about 3,500,000 per cubic millimetre (the average normal number of red corpuscles in the female is 4,500,000); the haemoglobin is

about 50 per cent., and the colour index is often about 0.5 or less.

There is, then, this striking difference between chlorosis and pernicious anaemia, that in chlorosis each red cell contains on an average about half the normal amount of haemoglobin, whereas in pernicious anaemia it contains more than the normal amount of haemoglobin. Consequently, the indication is to give iron in chlorosis; and we find, as a matter of fact, that iron is a specific in that disease. But if you give iron in pernicious anaemia, if you stuff the red cells, which already contain too much iron, with more iron, you do harm rather than good. There are, however, some cases of pernicious anaemia in which iron seems to do good, but they are quite exceptional. I have published some cases of this kind.

Intestinal antiseptics, such as beta-naphthol and bismarck, also have been tried, and in some cases the result has been satisfactory. Treating the mouth, removing bad and decayed teeth and stumps, keeping the mouth so far as possible in an aseptic condition, has been insisted upon by Dr. Hunter. It should certainly be done, for a bad condition of the mouth may do harm and cannot do good.

None of the remedies which have been used, with the exception of arsenic, have stood the test of a prolonged trial. Experience has, I think, shown that arsenic is the only remedy which up to the present time has afforded any real benefit in the treatment of pernicious anaemia, but its beneficial effects are in the great majority of cases only temporary.

Two or three years ago salvarsan was introduced by Ehrlich for the treatment of syphilis; it contains arsenic and mercury. After seeing the remarkable effects of this remedy in some cases of syphilis, I thought that possibly it might give as good or better results in pernicious anaemia than the ordinary arsenical treatment—Fowler's solution by the mouth. In giving arsenic by the mouth, I begin with small doses—2 minims of Fowler's solution, three times a day after food—and gradually increase the dose by an extra drop every fourth or fifth day until the maximum which the patient can take is reached. This dose varies greatly in different cases; it is 10 or 12 drops in most cases, and 16 or 20 drops in some cases, three times a day. I push the remedy until I find the maximum dose which the individual patient can take; I then go on with that dose for several weeks. In some cases intestinal disturbance, particularly diarrhoea, is produced even by small doses; I have found in these cases that by combining a small dose of morphine—an eighth of a grain or less—with each dose of the arsenic, the arsenic is usually quite well borne.

Further, one must remember that if one gives arsenic in large doses for a long period of time one runs the risk of producing arsenical neuritis—a very serious condition; I have seen it produced in several of my cases of pernicious anaemia. But some risks must be run. Pernicious anaemia, if allowed to go on, will certainly kill the patient.

I commenced the salvarsan treatment of pernicious anaemia in October, 1910—two and a half years ago—and have treated eleven cases with salvarsan, with, on the whole, most remarkably beneficial effects. I will show four of the patients and briefly describe the results in all of the cases.

CASE I.

A man, J. S., aged 49, married, an electric hoist man, formerly a soldier, was admitted to the infirmary in October, 1910; I had seen him in October, 1909, and had then prescribed arsenic by the mouth. He presented all the characteristic features of pernicious anaemia. The red blood corpuscles numbered 1,035,000 per cubic millimetre, the haemoglobin equalled 30 per cent., the colour index was 1.5. He had four injections of salvarsan (December 21st, 0.2 gram; January 5th, 1911, 0.3 gram; January 19th, 0.3 gram; February 9th, 0.3 gram.) I may say that I have in all cases injected the remedy into the gluteal muscles; in none of my cases has the intravenous method been employed. He was discharged from the infirmary on February 22nd, 1911, looking and feeling perfectly well; all the anaemic symptoms had disappeared. The red blood corpuscles were then 3,580,000 per cubic millimetre, the haemoglobin equalled 78 per cent., and the colour index was 1.1. He has remained quite well and has been working regularly ever since. I saw him last, on March 7th, 1912; the red blood corpuscles then numbered 4,580,000 per cubic millimetre, the haemoglobin equalled 94 per cent., and the colour index was 1. When I saw him last, on March 7th, 1912, he had, in consequence of the railway strike, to walk ten miles to get here in time for the clinic. He was perfectly fit and fresh after the ten-mile walk.

You will see that he looks quite well. He tells me that he has been quite well and working regularly every day since March, 1912.*

CASE II.

A woman, Mrs. P., aged 40, was admitted to the infirmary on November 15th, 1910, suffering from all the characteristic symptoms of pernicious anaemia. On November 15th, 1910, the red blood corpuscles numbered 990,000 per cubic millimetre, the haemoglobin equalled 30 per cent., and the colour index was 1.6. She had four injections of salvarsan (December 24th, 1910, 0.3 gram; January 7th, 1911, 0.3 gram; January 24th, 0.3 gram; February 9th, 0.3 gram). She made an uninterrupted recovery and was discharged from hospital on March 16th, 1911, looking and feeling well. Her red corpuscles then numbered 4,420,000, the haemoglobin equalled 94 per cent., and the colour index was 1.1. When her blood was counted last, on March 7th, 1912, the red corpuscles numbered 6,210,000 per cubic millimetre, the haemoglobin equalled 120 per cent., and the colour index was 0.97. Now this is the only case of pernicious anaemia I have seen in which the red corpuscles have gone above the normal as the result of treatment. I will now show you this patient, whom I have not seen for a year. She looks, you will see, the picture of health. She states that during the past year she has been perfectly well, with the exception of several attacks of biliary colic.

CASE III.

This case was a very severe one. A woman, Mrs. P., aged 56, was admitted to the infirmary on March 30th, 1911, apparently in a dying condition; the red blood corpuscles numbered 680,000 per cubic millimetre, the haemoglobin equalled 18 per cent., and the colour index was 1.3. She had two injections of salvarsan (April 6th, 0.3 gram; May 4th, 0.3 gram). All of us who watched the case were profoundly impressed with the remarkable improvement in her appearance and symptoms which followed the treatment; the red corpuscles went up to 1,020,000, the haemoglobin to 28 per cent., and the colour index was 1.4. She discharged herself on July 25th; she relapsed and died on September 5th, 1911.

CASE IV.

This was a remarkable case. A woman, Mrs. P., aged 41, was admitted to the infirmary on March 28th, 1911. The red blood corpuscles numbered 695,000, the haemoglobin equalled 16 per cent., and the colour index was 1.15. She had two injections of salvarsan (April 6th, 0.3 gram; April 21st, 0.3 gram). On May 5th she had to go home to look after her house and children, one of whom was ill. She was in poor circumstances, she had to nurse her sick child and do all her housework, washing, etc. On her discharge from hospital the red corpuscles numbered 1,495,000 per cubic millimetre, the haemoglobin equalled 34 per cent., and the colour index 1.2. Well, she went home; I never expected that she would improve, and did not hear of her again till May, 1912. She was unable to leave her children and come into hospital for further salvarsan treatment, and on May 23rd, 1912, I sent her a prescription for arsenic—2 minims of Fowler's solution three times daily. She only took two bottles of the medicine, and has had no treatment since. I have seen her from time to time. I was able, through the kindness of some friends, to get up a small fund in order to enable her to live more comfortably. She has made a splendid recovery. On January 18th, 1913, the red corpuscles numbered 4,060,000 per cubic millimetre, the haemoglobin equalled 74 per cent., and the colour index was 0.91. You will see that she looks remarkably well. She tells me that she feels perfectly well, and has since her discharge from hospital done all her housework without any assistance.

On March 1st, 1913, the patient wrote to me as follows: "In reply to your letter of the 28th February, I hope you will not be displeased when I tell you that I have only taken two bottles of the medicine, and just started to take the third one now. I have not been taking it constantly. Doctor, I thought I would just tell you that I have never had to call in the doctor for myself since I left the Royal Infirmary, and this is the first two years in my life, as far back as I can remember. It is out of a full heart of gratitude I thank you again for your great skill and kindness shown towards me and my humble home."

This is a very remarkable case, because when the patient was discharged from hospital she was very ill—profoundly anaemic, feet swollen, etc.—and she had to struggle on under great disadvantages.

CASE V.

A man, W. S., aged 50, was admitted to the infirmary on May 12th, 1911, suffering from profound pernicious anaemia. He had two injections of salvarsan (May 15th, 0.3 gram; June 19th, 0.3 gram). Slight improvement followed the first injection, but the improvement was only temporary; he died on June 24th, 1911. In this case the treatment produced no benefit.

CASE VI.

A man, P. S., aged 31, was admitted to the infirmary on May 17th, 1911, with very marked pernicious anaemia. The red blood corpuscles numbered 955,000 per cubic millimetre, the haemoglobin equalled 26 per cent., the colour index was 1.4. He had three injections of salvarsan (May 29th, 0.3 gram; June

12th, 0.3 gram; July 12th, 0.3 gram), but he did not improve, and went home, we thought to die, with his red cells numbering 600,000 per cubic millimetre, haemoglobin 19 per cent., and the colour index 1.6. In this case salvarsan seemed to do no good whatever while the patient was under treatment in the hospital. After going home, he remained semicomatose for ten days. He then began to improve and ultimately got apparently perfectly well. When I saw him on November 11th, 1911, he looked quite well; his red blood corpuscles numbered 3,100,000 per cubic millimetre, the haemoglobin equalled 66 per cent., and the colour index was 1.1. He had no treatment for the anaemia after leaving the hospital.

He remained in good health, without any return of the anaemia, until February, 1912, when he died from acute croupous pneumonia.

I am not going to affirm that this extraordinary improvement was the result of the salvarsan treatment, for we occasionally see cases of pernicious anaemia which show these very remarkable alterations and improve. At the same time I cannot altogether rid my mind of the idea that the salvarsan was, perhaps, the cause of the improvement, for in two cases which have proved fatal, and have been examined *post mortem*, the salvarsan was found to be encapsuled in the buttock, and much of it unabsorbed, even after a very considerable time. I think it is quite possible that the long-continued improvement which has resulted in many of the cases which I have treated with salvarsan is probably due to the slow and gradual absorption of the remedy. If that is so, the extraordinary improvement in this case may perhaps have been the result of the salvarsan treatment.

CASE VII.

T. S., aged 55, was admitted to the hospital on October 24th, 1911, suffering from profound pernicious anaemia. His red blood corpuscles numbered 790,000 per cubic millimetre, the haemoglobin equalled 27 per cent., and the colour index was 1.7. It was a very bad case indeed. He had one injection of salvarsan (October 27th, 0.3 gram), and a fortnight afterwards his red blood corpuscles had doubled—1,460,000 per cubic millimetre, the haemoglobin equalled 25 per cent., and the colour index was 0.8. He then unfortunately took an attack of bronchopneumonia and died.

Since I left this infirmary I have had some further experience in the salvarsan treatment of pernicious anaemia.

CASE VIII.

This was an extremely severe case of pernicious anaemia in a young man of 25; it was of three years' duration (it is very unusual for pernicious anaemia to develop at such an early age—22). It was one of the most severe cases I have ever seen. The patient was admitted to Chalmers Hospital on October 3rd, 1912; he had two injections of salvarsan (October 6th, 0.3 gram; October 12th, 0.3 gram); there was no improvement. He died on October 14th, 1912.

Now, in a severe case of pernicious anaemia—and the same statement applies to every grave organic disease—one must expect to find many failures from any plan of treatment, however successful it is in the great majority of cases. I do not claim that salvarsan will produce improvement in every case of pernicious anaemia, but I do say that it does produce remarkable improvement in a very considerable proportion of cases.

CASE IX.

A man, J. C., aged 72, was admitted to Chalmers Hospital on August 30th, 1912, suffering from very severe pernicious anaemia. His red blood corpuscles numbered 1,055,000 per cubic millimetre, the haemoglobin was 26 per cent., and the colour index 1.3. Although 72 years of age, he improved remarkably under this treatment. He had three injections of salvarsan (August 31st, 0.3 gram; September 14th, 0.3 gram; September 28th, 0.6 gram). He was discharged on November 27th, 1912; his red blood corpuscles then numbered 3,450,000 per cubic millimetre, the haemoglobin equalled 75 per cent., and the colour index was 1.

I intended to have brought this patient before you today, but I hear he is not well enough to come; whether it is simply a relapse of his old trouble or something else I do not know; but, be that as it may, the beneficial effects of the treatment in that case were very striking.

CASE X.

A man, J. T., aged 59, was admitted to Chalmers Hospital on December 12th, 1912, suffering from very profound pernicious anaemia with oedema of the feet, etc. His red corpuscles numbered 1,045,000 per cubic millimetre, the haemoglobin equalled 24 per cent., and the colour index was 1.14. He had two injections (0.3 gram of salvarsan on December 13th, 1912, and 0.3 gram of neo-salvarsan on January 9th, 1913). He is now quite well. He looks the picture of health. On February 14th,

* Cases I to VII are fully reported in the BRITISH MEDICAL JOURNAL, June 22nd, 1912.

1913, his red corpuscles numbered 3,900,000 per cubic millimetre, the haemoglobin equalled 86 per cent., and the colour index was 1.1. This is one of the most successful cases I have had.

CASE XI.

A man, J. R., aged 58, was admitted to Chalmers Hospital on January 11th, 1913, suffering from moderately severe pernicious anaemia. His red corpuscles numbered 1,690,000 per cubic millimetre, the haemoglobin equalled 48 per cent., and the colour index was 1.4. He has had two injections of neo-salvarsan (January 14th, 1913, 0.5 gram; February 14th, 0.5 gram). Up to the present time the improvement in this case has only been slight, but sufficient time has not yet elapsed to allow of a definite statement regarding the result. On February 6th his red corpuscles numbered 2,490,000, the haemoglobin equalled 67 per cent., and the colour index was 1.2.

CASE XII.

Another case, which is perhaps a case of pernicious anaemia, though the diagnosis is somewhat uncertain, is that of a man aged 42. He was admitted to Chalmers Hospital on December 16th, 1912, suffering from subacute combined paralysis and a moderate amount of anaemia (the red corpuscles numbered 2,750,000 per cubic millimetre, the haemoglobin equalled 80 per cent., and the colour index was 1.4). The high colour index is very suggestive that the anaemia is of the pernicious type. He has had two injections of neo-salvarsan (December 23rd, 1912, 0.4 gram; January 24th, 1913, 0.4 gram). There has been a slight improvement in the condition of the blood, but no improvement in the nervous symptoms.

I mention this last case as I am anxious to give my full experience—every case in which I have employed this treatment—whether the result has been satisfactory or not.

I have now given the results of eleven cases of undoubted pernicious anaemia, and of one doubtful case treated by salvarsan; of the eleven undoubted cases, four have been apparently completely cured—whether in these cases a relapse will occur or not I am, of course, quite unable to say; in two cases there was very striking improvement; in one case there was very considerable improvement, but ultimately a relapse and death; in one case there was slight improvement and death from bronchopneumonia while under treatment; in two cases there was no improvement; and in one case slight improvement, the patient being still under treatment. In the case of subacute combined paralysis associated with anaemia (perhaps pernicious anaemia), I tried the remedy as a last resource, though I did not expect it to beneficially affect the spinal lesion.

These results are very striking and very encouraging. I have had nearly forty years' experience of the ordinary arsenical plan of treatment of pernicious anaemia, and I have the greatest confidence in saying that the salvarsan treatment, so far as my present experience enables me to judge, is superior to the ordinary arsenical treatment. Further experience is, however, required before one can say whether the beneficial effects, which it undoubtedly produces in many cases, will be lasting or merely temporary.

In giving salvarsan I have always given it intramuscularly. In syphilis the usual way is to give it intravenously. In syphilis we know there is a definite organism, and we want to kill that organism as rapidly and as effectually as possible. In the treatment of syphilis the usual plan is to inject 0.6 gram of salvarsan into a vein. In primary and secondary syphilis the results are quite remarkable; relapses occur, however. The results in some of the tertiary cases are not so satisfactory as was at one time supposed. The results of salvarsan treatment in such conditions as tabes and general paralysis of the insane—parasyphilitic lesions—are practically *nil*. There have been different opinions expressed on this point, but I think the experience of the great majority of reliable physicians is that in tabes and general paralysis of the insane salvarsan is of little or no use.

In pernicious anaemia I have employed the intramuscular method of administration, for, in this disease, we want, I think, a remedy which will produce sustained and continued effects. We do not know what the toxin is which appears to be the cause of pernicious anaemia—whether a germ toxin or a chemical toxin. The dose I have always employed has been 0.3 gram, half the dose which is usually given in syphilis. In severe and advanced cases of pernicious anaemia, in which the patient's hold of life is very precarious indeed—and this was the condition in many of the cases I have brought before you—a very

little thing will turn the scale. I have therefore hesitated in these cases to give the remedy by the intravenous method.

In some cases the salvarsan, when given intramuscularly, produces very considerable inflammation, pain, and swelling; but the neo-salvarsan seems to be much more satisfactory in this respect—it does not produce such marked local results. In the cases in which I have used neo-salvarsan I have found that there is little or no local pain or hardness, and little or no rise in temperature. In the meantime I shall continue to give the remedy intramuscularly.

ADDENDUM (May 7th, 1913).

CASE IX.

This patient was readmitted to Chalmers Hospital on March 3rd, 1913, suffering from a severe relapse. The red blood corpuscles numbered 1,010,000 per cubic millimetre; haemoglobin 36 per cent.; colour index 1.7. As the result of two injections of salvarsan he has improved very rapidly; I fear, however, that as soon as he is again discharged another relapse will in all probability occur, and that the effects of the treatment will be merely temporary.

CASE XII.

During February, 1913, this patient rapidly got worse, the paralysis passing into the flaccid stage. He died on March 22nd. *Post-mortem* examination showed all the typical appearances of pernicious anaemia.

ACUTE PERFORATION OF THE GALL BLADDER:

WITH AN ACCOUNT OF SIX CASES.

BY

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In these days, when the early and exact diagnosis of acute abdominal conditions is a matter of extreme importance, it is essential to form a clear conception of the characteristic signs and of the methods of treatment of even the rarest forms of abdominal catastrophe.

Although McWilliams¹ and Cotte and Arnaud² have given such excellent descriptions of perforation of the gall bladder, in nearly all its varieties, there are perhaps some points of particular interest in the cases given below.

The effect of sterile bile in the general peritoneal cavity is to destroy the bactericidal quality of serum.

In rabbits Noetzel showed that whereas a certain amount of *Staphylococcus aureus* or *Bacillus coli* or streptococci placed in the normal healthy peritoneal cavity was innocuous, a similar amount was always fatal provided the bile from the healthy gall bladder was allowed to escape into the body cavity.

Normal bile is well tolerated for a considerable time, and becomes gradually shut off by inflammatory adhesions.

In a case recorded by Garré, operation undertaken two months after the injury which ruptured the gall bladder showed a localized and large collection of bile; the patient got well. In a case recorded by Hildebrandt operation was successful twenty-three days after a tear into the hepatic duct.

Bile which escapes from a rupture in a gall bladder containing stones is not an aseptic fluid, it teems with the *Bacillus coli* or other organisms.

It is in cases in which gangrene and rupture occur in an infected gall bladder that rapid and fatal peritonitis develops. Clearly the prognosis depends chiefly upon the number, character, and virulence of the organisms present in the bile.

McWilliams, omitting the purely traumatic variety, describes three kinds of rupture of the gall bladder:

1. Rupture from over-stretching; with or without stones.
2. Perforation from pressure of stone on the wall.
3. Perforation from gangrene due to:
 - (a) Thrombosis of vessels with or without stones.
 - (b) Cutting off of circulation from pressure of stone.
 - (c) Diphtheritic, ulcerative infection of the wall with or without stone.