suspicion of any harmful effect from the benzedrine occurred to him. No tablets were taken from June 25 to 28, and sleep even on these days was very restless. On each of the following four days one tablet was taken, and he travelled to London on June 30 for the practical part of the examination, which lasted three days. Severe headaches were again felt daily, and sleep was poor and restless. He returned home by a night train in the early morning of July 3 and, despite a feeling of utter weariness, was unable to sleep during the journey of six hours. At home he was observed to be very pale, and he complained of severe headache and giddiness, thirst, and a dry mouth. Although feeling thoroughly exhausted he was fully awake and unable to sleep.

In the early afternoon of the same day palpitation and a feeling of faintness supervened. He was given a small amount of brandy, when he improved and dozed for a few hours. He became restless again and began to vomit, and suddenly collapsed. The patient was seen at once by Dr. Milne, who found him unconscious and in a severe state of collapse. The pulse was extremely weak, rapid, and irregular, the pupils were dilated, and the skin was cold and moist: he was critically ill for one hour. Vomiting was profuse and of a projectile character for about thirty minutes. He responded fairly quickly to the usual measures of stimulation. Sleeplessness and restlessness were severe for the following three days, despite the use of simple sedatives. Gradual and continuous recovery then ensued, and he is now almost well again. There was no diarrhoea, and constipation was troublesome during the worst stage of his illness. Micturition was normal, except for being more frequent as a result of taking increased fluid for thirst. No haemorrhages occurred throughout the whole course of the illness.

Blood films were examined by Dr. Phillips on July 5 and a slight anisocytosis was the only qualitative change, apart from the poverty of the red cells in haemoglobin.

I saw him in consultation on July 9 and found him to be well nourished but very pale. No retinal or cutaneous haemorrhages were present, and no jaundice. There was slight general enlargement of the heart and fairly natural sounds, except for a haemic bruit in the pulmonary area. The pulse rate was 84, with regular rhythm; and the blood pressure 124 mm. Hg systolic and 50 mm. diastolic. The other systems were healthy, and the liver and spleen not palpable. The urine was normal. Unfortunately, a complete blood examination was impossible on that day. The haemoglobin, however, was 40 per cent., and some films showed much the same qualitative change as in the previous examination. The appearance of the patient corresponded with a red cell count of about two millions.

A full blood count was made a week later, when he was found to have improved in health as a result of the administration of full doses of ferri et ammon. cit. The result was as follows: Red blood corpuscles, 3,080,000 per c.mm.; haemoglobin, 56 per cent.; colour index, 0.9; white blood corpuscles, 5,400 per c.mm. The qualitative change was a little more marked than at my previous examination, and many of the red blood cells now showed polychromasia. No nucleated forms were seen, but there were a few myelocytes.

I saw him again on August 1, when he had improved still further. He was much less pale, and said that he felt almost well again. He was free from headaches, and sleep was good.

Another blood count was now done, with this result: Red blood corpuscles, 4,940,000 per c.mm.; haemoglobin, 94 per cent.; colour index, 0.9; white blood corpuscles, 6,800 per c.mm. The red blood cells were well stained and showed only slight variation in size. No polychromatic staining was seen. The white blood cells were present in normal proportions, but there were no abnormal cells.

Conclusion

A case of acute aplastic anaemia following the self-administration of benzedrine is described. The total amount taken was 190 mg. in the course of nineteen days.

Severe cardiovascular collapse occurred the day after the last dose was taken. Gradual recovery ensued, with restoration to normal health. The patient told me that the drug was being rather much used by students preparing for examinations. It is evident that the sale of this drug should now be strictly controlled by including it in the Schedule of Poisons.

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PERNICIOUS ANAEMIA WITH DIABETES MELLITUS

BY

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Though the combination of diabetes and pernicious anaemia is well recognized it is sufficiently unusual to merit study. The following case reports are illustrative.

Case I

A carpenter and joiner, aged 43, was known to suffer from pernicious anaemia with achlorhydria. He first came to hospital in July, 1936, when his blood count showed: haemoglobin, 52 per cent.; red cells, 1,900,000 per c.mm.; colour index, 1.3; white cells, 4,900; and a normal differential count. He was given pernaemon forte 4 c.cm. each fortnight and was making satisfactory progress, his blood count in February, 1937, being: haemoglobin, 95 per cent.; red cells, 4,800,000 per c.mm.; colour index, 1. For eighteen months he had been complaining of paraesthesiae of the feet, but there was no weakness, and no physical signs of cord involvement had ever been elicited. The urine had always been normal.

He was one of a family of seven, five of whom were alive and well. One sister had been admitted to hospital three months previously suffering from simple achlorhydric anaemia. Her blood count on admission was: haemoglobin, 25 per cent.; red cells, 1,600,000 per c.mm.; colour index, 0.8; white cells, 9,300; normal differential count. The gastric contents showed complete achlorhydria both to fractional and to histamine test meals, and the Wassermann reaction was negative. She was treated with blood transfusion and massive doses of iron, and was discharged, greatly improved, after three months' treatment, when the blood count was: haemoglobin, 75 per cent.; red cells, 5,000,000 per c.mm.; colour index, 0.75; white cells and differential count normal. The father had died at the age of 69 from heart trouble and dropsy; the mother was alive, aged 74, and suffered from simple goitre.

On March 16 the patient reported at the out-patient department complaining of the sudden onset of thirst and polyuria ten days previously. During this short period he had become very weak, had noticed increasing dyspnoea and giddiness on exertion, and had lost considerable weight. He was unable to eat owing to the dryness of his mouth, in spite of the fact that he was very hungry, and had found that his vision was becoming misty and his voice husky. On examination he looked ill and dazed, and he staggered slightly when walking. His temperature was 98.4° and his pulse rate 60. The physical examination was negative. There was no smell of acetone in the breath, but the urine was loaded with sugar and ketone bodies.

On admission to the ward his urine was found to contain 12 per cent. of sugar, his blood sugar was 716 mg. per 100 c.cm. (his last meal having been two hours previously), and his blood count was: haemoglobin, 80 per cent.; red cells, 3,500,000 per c.mm.; colour index, 1.4.

During the first twenty-four hours in hospital he received 240 units of insulin and 240 grammes of glucose. Thereafter he was treated with a diet containing 140 grammes of carbohydrate and 50 units of insulin daily; he also received 2 c.cm. of campolin every other day. Subsequently it was found possible to reduce the daily amount of insulin in a step-like manner until six weeks later his urine remained sugar- and acetone-free without insulin, and his sugar tolerance was within normal limits. He was discharged on May 4 with a blood count of: haemoglobin, 82 per cent.; red cells, 3,960,000 per c.mm.; colour index, 1.03. He was feeling remarkably well, and had put on one stone in weight.

While he was in hospital it was found that the gastric contents contained no free hydrochloric acid during a histamine test meal. Blood examination showed a sedimentation rate of 27 mm. in one hour (Wintrobe's method); haematocrit test 40 per cent.; corrected sedimentation rate 19 mm.; cell volume index 1.06; plasma cholesterol 164 mg. per 100 c.cm.; Wassermann reaction negative. The increased sedimentation rate remained unexplained.

The second case is less clear-cut, in that the condition of the patient whilst in hospital provided no opportunity for performing a test meal. The presence of achlorhydria, therefore, was never proved. Nor was any family history available. There are, however, enough facts to make the case worth recording if only to illustrate the onset of the diseases in the reverse order.

Case II

A retired nurse, aged 70, was known to have been a mild diabetic for at least a year. She had been in the habit of taking 20 units of insulin by injection night and morning, and of living on a slightly reduced carbohydrate diet. On this regime she had maintained comparatively good health, and her urine had only occasionally shown slight reduction of Benedict's solution.

On October 3, 1932, she was admitted to hospital complaining of increasing pallor, glycosuria, and thirst during the previous three weeks. She looked ill, and was dull and drowsy. Her mucous membranes were pale, her pulse 100 and weak, and her respirations rapid. A blood count showed: haemoglobin, 34 per cent.; red cells, 1,480,000 per c.mm.; colour index, 1.2; white cells, 3,600; and a normal differential count. The red cells showed anisocytosis and poikilocytosis, and both normoblasts and megaloblasts were seen. The average diameter of red cells by Pijper's method was 8.6μ , and the Price-Jones curve showed the typical shift to the right. The blood sugar was 500 mg. per 100 c.cm.; the urine contained 3 per cent. of sugar and much diacetic acid.

During the twenty-four hours following her admission she received in all 170 units of insulin and 170 grammes of sugar. She was taking fluids and passing urine well, and looked and felt better. Considerable difficulty was experienced in stabilizing her diabetes, and her blood sugar varied rapidly between 60 and 370 mg. per 100 c.cm. During the next

fourteen days, however, she was given 30 units of insulin daily, and her general condition improved considerably.

Shortly after admission she received a blood transfusion of 100 c.cm. and half a pint of gum saline intravenously, and thereafter one tube of liver extract and one phial of ventriculin were given daily. Three weeks after her admission her blood count was: haemoglobin, 40 per cent.; red cells, 1,315,000 per c.mm.; colour index, 1.5; and white cells 9,400.

Twenty-three days after admission she suddenly became ill with pulmonary congestion and died a few hours later.

Discussion

That diabetes and pernicious anaemia are sometimes found in association has often been remarked, and inquiry into the subject covers a period of twenty-six years. The best reviews of published cases are by Root in 1931 and again in 1933, and by Watson in 1933. Since then, however, few authors have written about it—Benjamin in 1934, Jolliffe, Brandaleone, and Most in 1935, and one or two more.

The first published report was by Parkinson as recently as 1910. He described the case of a man, aged 49, with pernicious anaemia who developed glycosuria, ketosis, and coma, terminating in death. At necropsy the characteristic findings of pernicious anaemia were disclosed. The pancreas was normal macroscopically and microscopically. Chvostek in 1918 was the next to describe a patient with both conditions, and in 1923 Giffen and Bowler alluded to two more in a paper reviewing the diseases that might be associated with pernicious anaemia. Two further cases were reported by Adams in 1925.

In 1931 Root made the first collection, which consisted of forty-eight cases: other reports followed, and in 1933 he collected another series of thirty-one. In the same year Watson added three more case histories and published an excellent review with a summary of the literature, and it is probable that at the time of the publication of this paper the total number of cases of combined diabetes and pernicious anaemia on record was seventy-nine.

That two so entirely different conditions should often be found in association is most remarkable, and frequent attempts have been made to discover a relation between them. The task, however, has not been easy, partly because of the difficulty of deciding which is the primary disease and which the complicating one, and partly because the incidence of the combination varies in different series of cases of diabetes and pernicious anaemia. There are, however, certain conditions common to both which might predispose to their simultaneous occurrence; and certain facts are known about alterations in carbohydrate metabolism in anaemic states which must also be taken into consideration.

The Primary Disease and the Complicating Disease

A point about which there is no clarity is whether the diabetes should be considered as a complication of the anaemia or vice versa. In Case I above the pernicious anaemia was known to have preceded the diabetes; in Case II it was probably the reverse; and in the majority of reported cases it was the diabetes that developed first. In two of Watson's cases the time of onset of the pernicious anaemia could not be stated with certainty as paraesthesiae were noted in the history before anaemia was suspected, and mild anaemia might have been present before the diabetes developed or before either disease was discovered. In one at least of Root's cases achlorhydria was found before any sign of anaemia.

Frequency

Some idea of the frequency of the association can be gained from various writers, but it varies in different series.

1. Watson found that in 949 diabetic patients of 25 years of age and over admitted to the Deaconess Hospital during the twelve months ending June 1, 1932, ten cases of pernicious anaemia occurred (1.05 per cent.).

2. Murphy and Moxon in 827 diabetics saw three cases of pernicious anaemia (0.36 per cent.).

3. In 370 cases of pernicious anaemia Wilkinson had four diabetics (1.05 per cent.).

4. The association was found in fifteen in a combined series of 2,461 patients with pernicious anaemia (0.61 per cent.) (Adams, Giffen and Bowler, Goudsmit, Joslin, Murphy and Moxon, Wright, and Wilkinson).

These figures are certainly suggestive of something more than chance, but no more than suggestive.

Factors Predisposing to Combined Incidence

Root has indicated some factors which may predispose to a more frequent combined incidence.

1. Achlorhydria is of fundamental significance in pernicious anaemia and often occurs in diabetes. The latter fact is perhaps not fully appreciated, but according to evidence adduced by Bowen and Aaron, Curtis, Ingram, Mason, Rabinowitch *et al.*, and Wohl, diminished or absent gastric hydrochloric acid occurs in 30 to 40 per cent. of diabetics. Hartfall found three diabetics among 336 cases of achlorhydria. This might prove to be a common aetiological basis.

2. The longer duration of life brought about by improved treatment might render a sufferer from one disease more likely to contract the other. It appears that the tendency to the development of defective gastric secretion increases with the duration of the diabetes and with the age of the patient. Since, moreover, the diabetes antedates the pernicious anaemia in most of the cases there appears to be some justification for regarding diabetics, in virtue of their prolonged existence, as more prone to develop pernicious anaemia.

3. The age factor.—No case has been observed in a young person. All occurred during the age period which is usual for the onset of pernicious anaemia and which includes the age most common for the development of diabetes.

4. Hereditary tendencies.—The familial tendency is well recognized in both diseases, and in one of the above reports the occurrence of a sister with achlorhydria and microcytic anaemia is a case in point.

Though these factors are common to both diseases, especially where diabetes is the primary condition, there still remain those cases where pernicious anaemia was the first to develop. In the latter circumstance certain changes in carbohydrate metabolism that are known to occur in anaemia seem more likely to be the agents which lead to the double pathology.

Conditions Favouring Development of Diabetes in Pernicious Anaemia

Davidson and Gulland, for instance, found some evidence that the achlorhydric stomach of pernicious anaemia empties rapidly, and in 1929 MacCullum suggested a hormone in the intestinal mucosa, formed under the stimulus of sugar, which controls the secretion of insulin. Since pernicious anaemia is a deficiency disease, other deficiencies of this nature possibly coexist.

Again, disturbance of sugar metabolism has many times been reported as a result of anaemia. As early

as 1877 Claude Bernard produced hyperglycaemia in dogs by repeated bleedings. Strauss reported an increased excretion of sugar in diabetics following venesection. Isaac and Hendrick found the blood sugar raised in pernicious anaemia, and Johnsson thought that the height of the blood sugar was related to the severity of the anaemia. In the same year, however, Blumenthal and Neuburger could find no definitely characteristic change and no connexion between the severity of the anaemia and the blood-sugar level. If it is true that changes in sugar metabolism of this nature occur as a result of anaemia, then it is quite conceivable that this fact has some bearing on the question of diabetes complicating pernicious anaemia. But a criticism that immediately comes to mind is that there is no evidence that the diabetes in all these cases developed during an anaemic phase. It certainly did not in the one reported above.

Finally, in 1929 Blotner and Murphy announced a blood-sugar-lowering effect following the oral administration of liver, though here again there has been no confirmation by other workers. Recently, however, Jolliffe, Brandaleone, and Most have reported changes in carbohydrate tolerance produced by high protein diets in two cases with the combined diseases.

Evidence, therefore, is contradictory, and no adequate explanation has yet been offered regarding on the one hand the mechanism of production of high blood sugar and abnormal sugar tolerance in pernicious anaemia, nor on the other the occasional occurrence of pernicious anaemia complicating diabetes. It is true that there is a certain amount of common ground between them, yet it appears that the only rational attitude is the one adopted by most authors—namely, that the phenomenon is a chance combination.

Summary

1. Two cases of combined pernicious anaemia and diabetes mellitus are described.

2. The history of knowledge concerning this association of diseases is given and the theories that have been put forward in explanation are discussed.

3. From a study of the literature no actual proof of aetiological relation is available.

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