J. O., a painter aged 47; admitted January 5th, 1914; died January 29th, 1914. He had had diabetes since March, 1913. Since then he had been on a strict diet. For the last fortnight he had complained of great lassitude. His eyesight had become bad. He had weighed 11 st. previously. On admission his weight was 8 st. 8 lb.; he was rather drowsy; his breath smelt of acetone. There was a small haemorrhage in the right retina, with some retinitis. The ferric chloride reaction was strongly positive. A diet containing 113 grams carbohydrate was given and sodium bicarbonate in large doses by the mouth and rectum (78 grams on January 7th). On January 9th ammonia N was 4.4 grams, index 13.6 per cent. He passed about 8 oz. (227 grams) sugar daily. On January 11th the urine was faintly alkaline. On January 13th ammonia N was 2.6 grams. He was now walking about the ward. The large doses of sodium bicarbonate were still continued. On January 22nd the patient's legs began to be oedematous. The sodium bicarbonate was diminished to 51 grams for three days, and it was then increased again to the previous amount. The oedema disappeared in twenty-four hours. On January 26th a normal full diet was given, with porridge and milk *ad lib.* On January 29th, 2 a.m., the patient suddenly had an attack of abdominal pain. He became delirious. He regained consciousness, and remained conscious right till his death, the next morning at 4 o'clock. While in hospital the alveolar CO₂ showed large variations—that is, between 2 and 5 per cent.

Post mortem.—Lipæmia, due to a finely divided suspension of fat. General wasting. Atrophied pancreas.

METHODS OF ANALYSIS EMPLOYED.

Sugar.—Benedict's method.

Ammonia.—By formal titration.

Ammonia Index (that is, the ratio between the ammonia nitrogen and total nitrogen).—The total nitrogen was calculated from the amount of urea, determined by Duprès's method, assuming that the urea nitrogen was always 96 per cent. of the total nitrogen. This is approximately the case under ordinary conditions of diet, and the results are accurate enough for clinical purposes. The Duprès method is much simpler than Kjeldahl's, and takes less time to perform.

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PAROXYSMAL HAEMOGLOBINURIA.

BY

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As the condition known as paroxysmal haemoglobinuria is of extreme rarity, and recorded observations may assist in its elucidation, I venture to set out some of the results obtained in an investigation of a case that has recently come under my notice.

The man, an ex-soldier, 42 years of age, who had re-enlisted for home service during the period of the war, was sent to me by the medical officer of his battalion on July 8th, in order to have his blood and urine examined, with a view to ascertaining if he was suffering from secondary anaemia and, if so, to what cause it could be assigned.

Well built and of keen intellectual capacity, he was, when I saw him, pale and bloodless, and his sclerotics were tinged yellow. He stated that he joined the army at the age of 19 years, and after six months' home service and six months at Malta was drafted to India, where he served eight years. He left India at the age of 28, and was then transferred to the army reserve. Whilst in India, at the age of 25 years, he contracted malaria—benign tertian—and also syphilis; for the latter he received oral mercurial treatment for a period of three months. After leaving the army he started work as a coal miner, and became successively a mine official and an inspector of mines. At the age of 33 he married, and six years later a girl was born, whom I have seen. She is now over 3 years of age, and appears perfectly healthy.

His general health has been excellent. Eight years ago, at the age of 34, he had an attack of what was diagnosed as influenza, with symptoms of pain in calves and thighs, and headache, but no rigors or "port-wine" urine.

In October, 1913, he formed one of an exploration party after the Senghenydd explosion. At one time, whilst returning to the base of operations, a distance of 1,000 yards, he and his companions were exposed for over two hours to smoke and gases. He himself felt great difficulty in breathing, and was unable to travel more than ten yards at a time. A fellow explorer suffered chiefly from pains in the head, calves, and thighs, with weakness of the legs—symptoms characteristic of CO poisoning.

Whether the effect of this exposure has played any part in my patient's subsequent illness it is difficult to estimate, but it is of interest to note that thereafter he complained of frequent tingling of the ears, only relieved by the application of warmth. His present illness, he told me, started eight weeks before with loss of appetite, constipation, frontal headache, lassitude, pains in the thighs and calves, some feverishness, and also some pain in the epigastrium. A fortnight later he experienced a slight "shiver," but no vomiting occurred at any time. During the last two weeks definite rigors developed, followed by profuse sweating. These rigors usually started about mid-day every day, and would last from two to five hours; they were not controlled by quinine. He noticed that the first appearance of "port-wine" coloration of his urine synchronized with the first rigor. From then to the time that I first saw him he had become steadily worse. About the time that the rigors started he first noticed that an irritating rash appeared on exposing his arms and legs when getting out of bed. The rash and its attendant irritation would last from twenty to thirty minutes, and on returning to bed and keeping closely covered the skin would assume its normal condition.

The specimen of urine he brought with him (July 8th) presented the following characters: "Port-wine" colour, acid, gave strong positive reaction with tincture of guaiacum and ozonic ether; high albumin content. On centrifuging, a heavy deposit containing very many granular casts, a few granular-leucocytic casts, and much detritus, all tinged a brownish colour. A few isolated leucocytes and urinary epithelial cells were seen. Some calcium oxalate crystals were present, but there were no red blood corpuscles.

I now proceeded to obtain some blood from the tip of the right ear. This procedure was immediately followed by a rigor. It will be noted that the blood taken on this occasion represented a sample of his circulating blood during the period of his haemoglobinuria. As subsequent events proved, this was the only sample I was able to obtain while he was in this condition, as, when I next saw him, he had improved so much that his immediate symptoms had ceased.

The blood withdrawn clotted quickly, and the resultant serum was large in amount. The serum was tinged a smoky-brown colour, with the very merest trace of a reddish tint. The Wassermann reaction was positive. A differential count of 300 leucocytes, performed at the same time, gave the following result: Polymorphonuclears, 70 per cent.; large mononuclears and transitionals, 7 per cent.; lymphocytes, 9.6 per cent.; eosinophiles, 10 per cent.; mast cells, 3.3 per cent. The leucocytes appeared greatly in excess of the normal ratio to the red corpuscles. There were a few dead leucocytes, chiefly polymorphs, eosinophiles, and mast cells. Blood platelets were present in slight excess. The red corpuscles stained lightly, rouleaux formation was fair; macrocytes, microcytes, poikilocytes, and many phantom cells present; polychromatosis abundant. No nucleated red corpuscles and no malarial parasites seen.

Four days later (July 12th), after his removal to the local military hospital, I was enabled to make continuous estimations of his urine over a period of eight days. Each time he micturated the total amount was measured, and a sample submitted to examination, in order to ascertain the question of acidity, specific gravity, general appearance and colour, and the presence or absence of haemoglobin, bilirubin, albumin and crystalline deposits. In this way it was possible to estimate the total for each successive twenty-four hours, and any changes that might occur.

The total daily amounts varied from 1,123 c.cm. to 1,746 c.cm.; the specific gravity from 1008 to 1028—even on the same day—but this variation was unusual, the average being 1016. The colour and appearance varied between a clear light amber and a cloudy deep brown; on no occasion did it show the slightest trace of a "port-wine" tint. Sometimes there would be a heavy deposit of urates, but there was never any haemoglobin present, whilst the slightest traces of bilirubin and albumin were only rarely encountered. It was surprising to find how extremely quickly the urine had approximated to the normal standard.

On July 12th I withdrew some of his blood. It again clotted quickly and produced a large resultant serum, which was, however, tinged a strong red colour. Using this serum in a fresh state I added it in varying dilutions to a 5 per cent. suspension of my own washed red corpuscles, with a suitable control, and incubated at 37° C. for one hour. No haemolysis took place in any of the preparations. The Wassermann reaction was positive.

On this day also I took 1 volume of the serum obtained on July 8th (immediately preceding a rigor), inactivated it at 60° C. for half an hour, to it added 1 volume of my own washed red corpuscles, 1 volume of my own fresh serum (complement), and 3 volumes of normal saline, incubating at 37° C. for one hour. As a result I obtained slight haemolysis of my own red corpuscles. I also, on the same occasion, took one volume of the serum obtained on July 12th (during the quiescent convalescent period), and proceeded in a precisely similar fashion, but I did not thereby obtain any haemolysis of my own corpuscles.

On July 15th I estimated his total leucocytes at 9,200 and total red corpuscles at 2,944,000 per cubic millimetre.

On July 26th I again withdrew some of his blood, the serum, as before, was strongly tinged. The Wassermann reaction was again positive.

On the same day I performed a differential count of 400 leucocytes with the following result: Polymorphs, 57.25 per cent.; large mononuclears and transitionals, 15 per cent.; lymphocytes, 20 per cent.; eosinophiles, 7.5 per cent.; mast cells, 0.25 per cent. The red corpuscles were much more uniform in size and shape, but there were still some macrocytes, microcytes, and poikilocytes, also some rosettes. The colour was better, but there was still some polychromatosis, though not so pronounced. A few shadow cells were present. Rouleaux formation was fair. There were fewer blood platelets, but many dead leucocytes, chiefly large mononuclears. There were no nucleated red corpuscles, and no malarial parasites were seen.

On July 30th I estimated his total leucocytes at 5,400 and total red corpuscles at 3,952,000 per cubic millimetre.

On this day also I made a preparation of his washed red corpuscles. To one volume of these I added one volume of his own fresh serum and one volume of normal saline, incubating at 37° C. for one hour. I further added to another volume of his own washed red corpuscles one volume of my own fresh serum and one volume of normal saline, also incubating at 37° C. for one hour. In neither preparation did haemolysis occur.

In order to ascertain if the haemolyzed state of his serum was due to free haemoglobin in the blood plasma (which seemed improbable, as his urine contained none) or to fragility of his red corpuscles, whereby the haemoglobin was expressed during the act of clotting, I withdrew on August 3rd one portion of blood, and allowed it to clot. The serum was definitely tinged with haemoglobin. Another portion of blood was received into a tube lined with paraffin wax and immediately centrifuged, thereby quickly separating the corpuscles from the plasma. The latter was seen to be entirely free from the slightest trace of tinting. In point of fact, it was perfectly normal in appearance.

A curious phenomenon was noted in the right ear. On the day following the first needle puncture the site of the puncture in the lobe, together with the upper portion of the ear, which had not been punctured, became tense and swollen with extravasated blood and tender to the touch. Thereafter the left ear was used, happily with no untoward result. The right ear assumed its normal state in the course of two to three weeks, the normal condition being hastened by keeping the ear protected and warm.

During the course of the investigation he was at first kept strictly in bed, on a milk diet. Then, when it was

found that his urine remained free from albumin, eggs were allowed; later, fish and a full diet.

Throughout he was extremely susceptible to cold. Although to the ordinary mind the temperature was distinctly warm (75° F. in the shade), he would be found with as many as nine blankets and woollen coverings, including his great coat!

During this time his temperature fluctuated between 97.4° F. and 99° F. When he began to sit up he complained of considerable pain in the thighs and calves, though this, in time, passed off. Eventually he improved sufficiently to allow his return to his billet, and his convalescence is proceeding satisfactorily. Iron and arsenic are being given to combat the anaemia. It would be inadvisable to administer neo-salvarsan intravenously until his corpuscles have regained their normal state.

In reviewing the facts disclosed, one is first of all struck with the malarial and specific history, a combination of frequent recorded occurrence in the etiology of paroxysmal haemoglobinuria, though the disease has been described when neither the one nor the other has been antecedent. The next point is that the first symptoms should have started in midsummer, as it is generally held that exposure to cold is a predisposing factor. In this case there was not even the possible exposure to the rigours of camp life, since he was billeted and his work was actuarial. I did not go the length of deliberately exposing him to cold in order to test this contention, but I understand from the medical officer of his battalion that on arrival at his billet, after a twelve-mile drive in the ambulance, he experienced a slight rigor. The vasomotor disturbances, as seen in the right ear and in the exposure rash, are of interest in connexion with the previous history of tingling in the ears, relieved by warmth, subsequent to exposure to CO fumes.

The blood counts are of interest chiefly as supporting the condition of secondary anaemia following the loss of blood indicated by the haemoglobinuria. For some reason the eosinophilic count was high. The process of approximation to normal in the case of the urine was remarkably rapid and very difficult to understand.

As far as the blood serum is concerned, the suggestion is offered that the marked haemolysis present, after the period of the rigors and haemoglobinuria had passed, is evidence of the fragility of the red corpuscles, the haemoglobin being discharged from them during the act of clotting, since the plasma prepared coincidentally was normal in appearance. However, this does not quite explain why the serum of the blood taken immediately prior to a rigor, and during the period of the haemoglobinuria, should have been but barely tinged with haemoglobin; its smoky-brown colour strongly suggests reduced haemoglobin.

The presence of a haemolytic body in the serum just prior to a rigor, and coinciding with the period of haemoglobinuria, and its absence later, coincident with the cessation of haemoglobinuria, are points of some importance.

In a short note on "Psychological Medicine," published in the Educational Number last week, p. 385, it should have been stated that the University of Manchester grants a diploma in psychological medicine. We regret the oversight the more because the University of Manchester was, we believe, the first to give such diplomas.

In a paper on the experimental treatment of human beri-beri with constituents of rice polishings (*Philippine Journal of Science*, March, 1915) Williams and Saleeby come to the conclusion that allantoin has a beneficial effect in certain cases of beri-beri, although it probably never produces complete cure. Hydrolyzed extract of rice polishings has been found to benefit all the types of the disease upon which it has been tried, and unhydrolyzed extract of rice polishings is, they state, a safe and valuable remedy for infantile beri-beri, but of little use for older cases. The vitamins of rice polishings was proved to possess specific and prompt curative properties far beyond those of any other known substance, but unfortunately its cost at present prohibits its general use amongst the poorer class. As a whole the observations on the 27 cases recorded in this paper are, as regards their bearing on the etiology of beri-beri, in accord with the broad proposition that the disease, in a practical sense at least, results primarily from a poor diet, deficient more particularly in specific substances of the nature of Funk's vitamins.