Remarks

ON

CHRONIC SPLENOMEGALIC
POLYCYTHAEMIA.*

BY

ROBERT SAUNDBY, M.D., M.Sc., LL.D., F.R.C.P.,

PROFESSOR OF MEDICINE IN THE UNIVERSITY OF BIRMINGHAM;
PHYSICIAN TO THE GENERAL HOSPITAL.

THE disease, which has been called by various names, but which at least temporarily we may agree to call by the name given it by Dr. Parkes Weber, "chronic megalosplenic polycythaemia," may be defined as a chronic progressive asthenia, characterized by debility, high blood pressure, general redness or cyanosis of the skin, splenic enlargement, polycythaemia affecting the red cells with a proportional rise in the percentage of the haemoglobin the specific gravity and the viscosity of the blood, but without any increase of the white cells.

There may be periods of remission during which the subjective symptoms disappear and the patient feels well. Later cyanosis, dyspnoea, oedema of the lower extremities, dilatation of the heart, enlargement of the liver and albuminuria occur, and may be associated with mental depression or dullness, apathy and drowsiness.

The course appears to extend over many years (seven or eight), but the tendency is to terminate ultimately by gradual heart failure or by cerebral haemorrhage. Out of 46 recorded cases, 26 were males and 20 females. The oldest case reported was 61 (Hall, female), the youngest 20 (Ascoli, male); the average age was 43.

It has only attracted attention during the last few years, and its history may be briefly related. So long ago as 1892 Professor Vaquez, working at the blood condition in cyanosis due to congenital disease of the heart, came across a case which he published under the impression that the cyanosis depended upon a congenital heart lesion. There was enlargement of the liver and spleen. The red corpuscles were increased in number and there was a proportional rise in the haemoglobin, but it was not until 1895 that he discovered at the death of the patient the absence of any cardiac affection. In 1899 Widal and Rendu brought forward a case of a man who had an enlarged spleen, marked cyanosis, and polycythaemia. After death the heart was normal, but the spleen was tuberculous and contained large caseated areas, and the bone marrow showed nucleated red cells pointing to overactivity. In the same year Cabot of Boston published 2 cases in the *Boston Medical and Surgical Journal*, and another case was published in 1901 in the same journal by McKeen.

CASE I.

On April 24th, 1891, during the course of an influenza epidemic, a man named T. H., silversmith, aged 48, was admitted under my care, complaining of pains all over the body, especially in the abdomen, and of general illness. His evening temperature was 102° F.; pulse, 96; respirations, 24; and he said that his present illness had commenced only four days previously. We attributed, and probably rightly enough, these acute symptoms to an attack of the prevailing epidemic, but we discovered that his spleen was enlarged down to the umbilicus (as shown in the diagram), although there was nothing in his history to explain its enlargement. He was discharged on May 16th, although still weak, and had to be readmitted on June 9th, when his temperature in the evening was again as high as 101°. He complained of great weakness, inability to work, and said he could scarcely get about. On examination the spleen was found to have diminished greatly in size (as shown in the diagram). We regarded the asthenia as still a probable result of influenza, and sent him to the Sanatorium for fourteen days.

According to his own account he recovered completely, and remained well until 1897, when he again began to suffer from great weakness with pain in the abdomen, made easier by lying down. Towards the end of the year he became so ill that he gave up his work, and on January 29th, 1898, he attended at the hospital as an out-patient, where he was seen by Dr. Russell, who had been resident medical officer when he was an in-patient seven years previously. Dr. Russell remembered him, and being glad of the opportunity to follow up a case which had been somewhat of a mystery, he directed him to be

admitted under me. The patient complained chiefly of pains all over him, but especially in the right side and in the head, of a fortnight's duration; but lately he had been getting weaker and thinner, so that he could hardly stand and could not walk to his work; about a fortnight before, having had occasion to get out of bed, he fell on the floor and lay there all night, unable to get up; since that time he had remained altogether in bed, although with the aid of an omnibus he had been able to get to the hospital.

When we saw him the most striking feature in his appearance was the very marked cyanosis. The skin of his face was deeply congested and cyanosed; his nose was enlarged, thickened, very blue, and covered with dilated veins; his ears, lips, and cheeks were blue; his fingers were slightly clubbed, with incurved nails; the skin of the arms and hands was thin, soft, and cold, while around the joints it was bright red. He looked very depressed; his memory was evidently failing, as he was unable to recollect events in his history which had been recorded in our notes on his previous stay in the hospital; his speech was slow, thick, and mumbling, and he is described by the clerk who took the notes as "like a man the worse for drink." His tongue was very red; his teeth were mostly missing; his liver was $\frac{1}{2}$ in. below the costal margin; the spleen reached to the middle line and to the level of the

Case I.

April, 1891.

June, 1891.

March, 1898.

April, 1898.

umbilicus, and was hard but not tender. The heart was not enlarged; pulse 96; tension "higher than normal"; vessels everywhere very prominent and thickened; knee-jerks absent.

Blood:	Red Corpuscles.	Haemoglobin.	Leucocytes.	Spectrum.
February 5th	8,540,000	140 %	Not increased	Normal
February 8th	8,833,000	—	—	—
February 13th	8,483,000	—	—	—
February 18th	9,260,000	—	—	—
March 8th	8,900,000	140 %	Not increased	—

He was sent out on March 20th, but readmitted on March 24th, and when he was seen he was found to be deeply cyanosed and jaundiced, drowsy, apathetic, and passing his urine in the bed. The fingers, ears, cheeks, nose, and skin of his back are described as being of a purplish colour; temperature 99°. In spite of the jaundice, the urine contained no bile, and, according to Dr. Powell White, now of Manchester, then Resident

* Read before the Birmingham Branch of the British Medical Association, March 14th, 1907.

Pathologist to the General Hospital, there were no abnormal pigments in the urine, and the stools were dark brown. The red blood corpuscles numbered 7,360,000; the spleen was rather smaller (as shown in diagram). On April 2nd a note is made that "the abdominal tumour (spleen) seems to be increasing in size and extends now to the right of the middle line" (see diagram). I would draw your attention to the remarkable variation in the size of the spleen, which has also been noticed in the case to be shown to-day. The patient grew gradually more drowsy and more intensely cyanosed, but the jaundice was less marked. He died on April 9th.

At the *post-mortem* examination nothing was found to throw any light upon the case; the heart was somewhat enlarged with "old disease of the mitral valve"; the internal organs were congested; the spleen weighed 48 oz., but on section appeared normal. The marrow of the femur was examined and showed no naked-eye change, but was not examined microscopically.

Four years afterwards Dr. Russell published this case, and by so doing acquired the right to claim it as the first example of the condition which had been observed in this country.

CASE II.

The patient I propose to show you to-day, G. Y., came originally under my care on February 23rd, 1905, complaining

Case II.

of swelling of his legs, which had followed an attack of influenza four months previously. At that time it was noted he had a ruddy complexion, that his tongue was coated and "blue," and that there was universal reddish congestion of the skin. On standing up the congestion of his legs was more marked, and the veins became distended with blood. He complained a good deal of pains in his legs and walked with great difficulty. There was no enlargement of the spleen, and no blood count was made at the time; in fact, the case was regarded as being possibly due to thrombosis of the inferior vena cava following influenza. After a week's rest in bed the swelling of the legs disappeared, but they remained painful up to the time of his leaving the hospital on March 26th. Although better he was never able to resume work, and he continued to attend as an out-patient under Dr. Russell. He was readmitted in March, 1906, for a return of the swelling of the legs with inability to walk, and he had lately noticed swelling of the abdomen.

Up to the commencement of this illness he had always enjoyed good health and had had plenty of good food. He used to drink three pints of beer a day and sometimes more, and smoked about half an ounce of tobacco a day. There was nothing in his family history to suggest tubercle.

At that time he is described as presenting a florid appearance, the veins of his forehead being prominent; as he lay in bed he sighed occasionally, and seemed short of breath when speaking. There was oedema of the walls of the chest and abdomen as high as the axillae, and the legs were swollen, the skin being shiny and bluish-red. On standing up the veins of the legs became distended with blood; knee-jerks absent.

The heart's apex was $\frac{1}{2}$ in. outside the line of the nipple; the sounds were pure, the pulse regular, 80, and the blood pressure 170. His liver reached halfway to the umbilicus, and the spleen could be felt below the costal border. The urine contained a trace of albumen; ophthalmoscopic examination of the eyes showed only fullness of the retinal veins. Examination of the blood showed:

Red blood corpuscles 8,320,000.

Viscosity, mean of three estimates by Dr. J. H. Watson, 9.4 (normal blood 4 to 5).

Haemoglobin 140 per cent.

Differential count normal.

He was treated mainly by rest, and ultimately made an out-patient on June 6th.

Late in October the legs were very much swollen. He was advised to rest as much as possible, and readmitted on October 23rd, by which time the oedema had gone. The displacement of the apex beat had become more marked, being 1 in. beyond the line of the nipple. The first sound is described as obscure and the second as sharp; pulse 84, giving the blunt-headed curve of high tension; blood pressure 180.

Blood Count.	Red.	White
October 27th	7,600,000	7,000
November 18th	8,400,000	9,000
November 24th	9,200,000	11,000
December 7th	8,400,000	—
December 16th	8,600,000	—
December 24th	8,500,000	—
January 6th	8,200,000	—
January 27th	7,144,000	10,200
February 6th	7,896,000	—

No abnormal red cells; differential count of leucocytes normal.

Haemoglobin	December 11th	190
"	January 4th	180
"	January 27th	160

Specific gravity, taken several times, November 25th, 1080; two other occasions, 1075; haemolysis 40.

Blood coagulation, January 6th, 8 min.; January 15th, 10½ min.

Both liver and spleen were considerably enlarged and easily felt below the costal border, but varied in size from time to time (as shown in the diagrams).

The urine always contained albumen, which was serum albumen and not globulin; the daily amount of urea was on an average 370 grains; urobilin was generally absent, but was present on November 15th (Mr. L. C. S. Broughton); a large quantity of indican was always present; there was no blood; casts were repeatedly looked for, but never found. Well marked dermatographism was always present. He was discharged on January 8th of the present year, and readmitted for further examination on January 27th.

His treatment has varied from time to time, according to our wavering views as to the cause of the disease. At first he was kept in bed, and when his legs were weak faradism was used for the muscles. He has been given iron, arsenic, digitalis, adrenalin chloride, quinine, diuretin, and he has been bled to 12 oz. with temporary relief. His colon has been irrigated systematically with large quantities (5 to 6 pints) of water, which for some time contained 5 grains of alpha-naphthol to the quart; the only noticeable effect of this last means was to reduce the quantity of indican in his urine which was persistently present.

We have lately been keeping him upon four-hourly doses ($\frac{1}{4}$ grain) of erythrol tetranitrate, in the hope that we might relax the spasm of his arterioles, but without much benefit, so that it is to be feared the vessels have become thickened and narrow. We have also tried the administration of vinegar in $\frac{1}{2}$ oz. doses three times a day, in order to test the popular belief that vinegar drinking makes people pale. The result is to be seen in the blood count made within the last few days:

March 10th. Red cells, 6,800,000; haemoglobin, 150; coagulation time, 8 minutes; haemolysis, 42; blood pressure, 130.

March 13th. Red cells, 7,440,000; leucocytes, 11,800; haemoglobin, 165; specific gravity, 1075; blood pressure, 140; pulse, 72.

Although the red cells show some diminution the number is not materially less than it has been previously, and cannot with certainty be attributed to the treatment. The reduction in blood pressure is undoubtedly due to the use of erythrol. The interval after the dose was on March 10th 30 minutes, and on March 13th 135 minutes. So far there is no evidence that the vinegar has produced much effect, and it is at least doubtful whether the patient would be benefited if we could administer a remedy which favoured the destruction of his red blood cells, but it seemed worth while to test the popular belief.

I should like, before concluding this account, to emphasize the fact that no abnormal red cells have ever been seen in either of my cases.

In 1902 Dr. Pierre Quiserne, a pupil of Professor Vaquez, published his thesis for the doctorate upon this subject, and collected together a number of cases with other information bearing on the subject. Some of these cases were

brought before the Association of American Physicians in 1903 by Professor William Osler, and in 1904 he published a paper in the *BRITISH MEDICAL JOURNAL*, in which he summarized 17 cases and pointed out that while some were undoubtedly associated with tubercle of the spleen, others were not so affected, and that the disease could not rest upon that foundation. He suggested the desirability of carefully studying the heart, the lungs, and the specific gravity and viscosity of the blood in these cases, as he expressed his belief that the cyanosis probably depends upon the increased difficulty of the flow of blood through the capillaries.

In 1904 Drs. Parkes Weber and J. H. Watson published a carefully-noted case, with *post-mortem* examination, in which they found evidence of proliferation of the bone marrow, a condition regarded by them as primary and the cause of the disease.

In 1905 Drs. Begg and Bullmore reported a case in the *Edinburgh Medical Journal*. Dr. Parkes Weber has since published a very elaborate study of the clinical features of another case, and Dr. R. Hutchison and Dr. Miller have published the notes of a case (1906) that died in the London Hospital where the occurrence of proliferating bone marrow was also observed.

The condition was the subject of a discussion at the Berlin Medical Society last winter, being introduced by Professor Senator, who accepted the bone-marrow theory of its origin. This brings the subject sufficiently up-to-date for our present purpose.

The various theories to account for the phenomena that have been put forward are:

1. *Primary Over-production of Red Cells in the Bone Marrow*.—This was originally observed by Vidal and Rendu in 1899, and is supported by Breuer (1903), Parkes Weber and Watson (1904), Türk (1904), and Senator (1906); the last suggested that diminished destruction may also play some part. This theory rests on the fact that the bone marrow in several cases has shown signs of proliferation, but this may be seen in the compensatory polycythaemia of congenital heart disease (E. Weil).

2. *Stasis*.—This explanation is accepted by Reckzeh (1905), Grawitz and Lommel (1906). They do not state how it is produced, although the presumption is that Grawitz would refer it to vaso-constriction, and Lommel speaks of "viscosity." If by stasis is meant the obstruction to the circulation caused by arterial hypertonicity or vascular spasm, then it is with them that I desire to range myself, and I will proceed to give in detail the evidences of the existence of this vascular spasm, and the proof of its being a sufficient cause of the changes observed in the blood and the other dependent symptoms.

3. *Diminished Respiratory Capacity of the Blood*.—This is the theory of J. Bence and Koranyi; Parkes Weber says that Boycott endeavoured to ascertain the respiratory capacity of the blood in two cases, and found it in one equal to, and in the other 10 per cent. greater than, normal, but Parkes Weber rightly observes that if it were proportional to the number of red blood corpuscles present it would have been much greater than normal, and the results so far as they go indicate that the individual blood corpuscles possess a diminished respiratory power.

4. *Diminished Destructibility of Red Blood Corpuscles*.—No one has been so bold as to put forward this explanation for the entire increase in the number of red cells, but it was suggested as possibly playing some part in the result by Gibson, Parkes Weber, Watson, and by Senator, but Gibson subsequently receded from his position in a published letter, and in a subsequent case which was examined for Dr. Parkes Weber by Sir A. E. Wright the haemolytic index was said to be normal. As the condition is certainly competent to play an important part did it really exist, it seemed worth while to test it thoroughly, and in order to do so I adopted a method described by M. Ribierre in his thesis on haemolysis and the measure of globular resistance applied to the study of the globular resistance in jaundice. A 0.50 per cent. solution of chloride of sodium in distilled water is placed in a series of little tubes; the first contains fifty drops; the second forty-eight drops with two of distilled water; the third forty-six drops with four of distilled water, and so on, each tube containing two drops less of salt solution and two drops more of distilled water. Into each tube is placed the same quantity of diluted blood. Normally haemolysis commences in the tube containing forty-four

drops of salt solution, and is complete in five or six tubes. In jaundice, however, the resistance is increased, and commences in the tube containing thirty-eight or thirty-six drops. In some blood diseases, however, haemolysis, or the tendency to haemolysis, may be so great that the percentage of salt solution must be 0.60 or 0.70.

We have at present in the hospital a man named F. H., aged 48, suffering from obstructive jaundice. His red blood cells are 4,420,000, and the leucocytes 8,600. His haemolytic index is from 0.38 to 0.32, so that there is a considerable reduction of the destructibility of the red cells but no corresponding increase in their number. On the other hand Dr. Mackey has made several estimations of the haemolytic index in G. Y.'s case and has found it on each occasion to be 0.40, so that there does not appear to be any notable diminution of destructibility, certainly not anything that could be invoked to play an important part in the production of polycythaemia. I ought to mention that the quantity of blood used from G. Y. in these estimations has been proportionally less than normal blood and in accordance with the amount of haemoglobin present.

The name "polycythaemia" has, of course, been given to this disease on account of the great increase of the red cells of the blood, which is found on examining a suitably diluted drop of blood taken in the ordinary way and with the usual precautions from the lobe of the ear. But it has been found that an abnormally high blood count, equal to that which has been seen in these cases, may be met with in various conditions. In the first place, Malassez proved that venous or capillary blood is richer in corpuscles than arterial blood, and he insists upon the influence of the vasomotor system in determining the richness of the blood in cells and haemoglobin. Further, as might be expected, the venous blood returning from a gland where the blood has parted with a considerable quantity of water, shows marked polycythaemia. Thirdly, the effect of vasomotor changes was demonstrated by Zuntz and Cohnstein, who showed that, while section of the cord high up leads in a few minutes to a fall in the number of red cells from 5,000,000 to 3,000,000, stimulation of the cord determines an afflux of cells, so that the capillaries of the skin become gorged with blood and the cells are so packed together as to cause stasis by arrest of the circulation. The influence of the vasomotor system in producing concentration of the blood is also supported by the results obtained by Grawitz, who found that when the vasomotor nerves were stimulated by cold or friction, the specific gravity of the blood was increased. Finally, there is a curious experiment described by Cheron: When to an anaemic and neurasthenic subject is administered an injection of a simple artificial serum (from 5 to 10 c.cm. of a 1 per cent. chloride of sodium solution), the number of blood corpuscles having been first counted, the proportion of haemoglobin ascertained, and the arterial tension measured, the result is: (1) A marked increase in the arterial tension; (2) an increase in the number of blood corpuscles, which frequently amounts to the addition of one-fifth, one-fourth, or even one-third of the original number, according to circumstances. Under the influence of the stimulation by the hypodermic injection of the entire circulatory apparatus through the central nervous system the blood vessels are contracted, their capacity is lessened, the liquid portion of the blood is squeezed out into the perivascular tissues, and the red blood corpuscles, circulating in a much smaller quantity of liquid, appear to be much more numerous in a given space. We have repeated this experiment several times with definite positive results.

In such circumstances no one can suppose that there is a sudden enormous overproduction of the red cells, amounting in some cases to double the normal number; but the polycythaemia is due to local concentration of the blood, and is therefore spoken of as being apparent and not real. Permanent and real polycythaemia has been observed in congenital heart disease (Vaquez, Gibson, Weil), in stenosis of the trachea or larynx (Labbé, Quiserne), in the blood of persons living at high elevations; in all these circumstances it is supposed to be due to impaired haematosis—or, in other words, is compensatory to diminished supply of oxygen to the tissues. These clinical results have been confirmed experimentally by compressing the trachea (Vaquez, Sellier), by causing partial pneumothorax (Auscher and

Lapique), and by diminished supply of oxygen (Sellier), while conversely, in pure oxygen the number of red cells falls rapidly (Regnard).

There are two questions that must be answered respecting the polycythaemia in the present group of cases—first, have we to do with a *real* increase in the total number of red cells in the body, or is this only apparent and the consequence of the accumulation of red cells in the capillaries of the skin? secondly, if it is *real*, is this increase of red cells *primary* or secondary to some other condition?

The strongest arguments in favour of the reality of the increase are (1) that the total mass of the blood is increased, and (2) that the marrow of the long bones is in a state of unusual functional activity. The estimation of the total mass of the blood was made by Professor Haldane on two occasions in one of Parkes Weber's cases, when it was found to be nearly double the normal amount. The method adopted is that invented by Professor Haldane and Professor Lorrain Smith; it is based on the determination of the quantity of carbonic oxide required to saturate the whole of the blood; for example, if it is known that it requires x quantity of carbonic oxide to saturate a unit of blood, and it is found that an individual requires to inspire $50x$ in order to determine a certain colour change in a drop of his blood, the total quantity of his blood will be equal to 50 units. If, as these authors say, the saturation of the blood occurs practically instantaneously, and that it is easy to measure the amount of gas required, their conclusions seem to be logically correct. I have not been able to get G. Y.'s blood examined by this method, but it is most desirable that there should be other determinations made, as it is at least unsatisfactory to allow such an important conclusion to rest upon the data of one case.

The accompanying drawing is from a photograph of films of the bone-marrow prepared by Dr. James Miller from a case of cyanosis and congenital heart disease in a child aged 4, who had been under the care of Dr. Stacey Wilson in the General Hospital.

The marrow was taken from the centre of the shaft of the femur, stained with haematoxylin-eosin, and is multiplied 570 diameters. It shows numerous red nucleated cells with small deeply stained nuclei, numerous myelocytes and large cells with large pale nuclei, and also several eosinophile myelocytes with coarse granules in their protoplasm. Dr. Miller adds in his note that the presence of actively functioning red marrow in the shaft of the long bone is in the adult an abnormal condition, while in the child at birth red marrow is normally present and is gradually replaced by the yellow fatty marrow characteristic of the adult, but so far as he has been able to investigate the question active red marrow is present in the shaft of the femur up to the age of 3.

The reason for considering the blood change to be primary appears to be, so far as I can follow Dr. Parkes Weber and those who agree with him, that the proliferation of the bone marrow must be primary because no other

lesion present could determine it as a functional reaction or compensation, as in congenital heart disease.

This overlooks or underrates the importance of the stagnation in the capillary circulation with dilatation of all the small blood vessels of the skin, the fullness and increased pressure in the subcutaneous veins, which are not the consequence of polycythaemia, as is proved by their absence in that which occurs in high places. If, on the other hand, they indicate, as I believe they do, impaired peripheral circulation, defective supply of arterial blood, a generalized "asphyxia" of the skin, there is a sufficient cause to explain the compensatory reaction of the bone marrow.

The condition of this patient's skin may be compared to the red face of the coachman, of which the accepted explanation is that under the influence of constant stimulation by cold, perhaps aided by alcohol, the middle-sized arteries are contracted, while the capillaries are dilated and engorged with blood. Wherever this occurs there is increase of red blood corpuscles, of haemoglobin and of specific gravity, with necessarily greater viscosity, so that not only is the force of the heart partially shut off by the

stopcock action of the middle-sized vessels, but the condition of the blood must obstruct its flow through the capillaries. The immediate local effect is "asphyxia" of the skin, but this ultimately stimulates the bone marrow to abnormal activity, increases the number of red cells, raises the specific gravity and viscosity of the blood, and creates a vicious circle by which the existing conditions are aggravated and the difficulties under which the heart maintains the circulation are perpetuated.

It will be seen from the figures given in the notes of G. Y.'s case, that the leucocytes showed no increase, but were proportionately rather diminished. But in the discussion which took place

Photograph of film of bone marrow from femur of child, aged 4, with cyanosis and congenital heart disease, showing numerous nucleated red cells and myelocytes. $\times 570$; haematoxylin-eosin.

at the Berlin Medical Society, Senator is reported to have spoken of an increased formation of leucocytes; the absence of this increase is to a certain extent opposed to the hypothesis of primary functional activity of the bone marrow; for there is no reason why a primary affection should not extend to both kinds of blood cell; if, however, the formation of new red cells were a compensatory effort in the presence of impaired haematoses, it is in accordance with analogy that Nature would supply the kind of cell required and no other.

If it must be admitted that there is no direct evidence of the polycythaemia being primary, and if the main argument relied upon is the alleged absence of any other sufficient independent cause which could constitute a hindrance to the circulation, we must inquire how far this latter statement is true.

The *post-mortem* examination of our first case showed that the heart was enlarged with old mitral valvular disease, and thickening of the left ventricle (Dr. Russell is sure that there was no marked disease of the valve); the present case shows evidence of cardiac dilatation; in Parkes Weber's first case there was some hypertrophy of the left

ventricle with atheroma of the aorta and aortic valve; and in Hutchison and Miller's case the heart was enlarged and the myocardium fibrous; yet none of these changes is of sufficient magnitude to account for the stagnation of blood in the capillaries, and we must look elsewhere for an adequate explanation. There is an entire absence of any evidence of obstruction to the return of the venous blood to the heart, such as would account for the distension of the veins and the sluggishness of the venous circulation.

The cause must be looked for in deficient *vis a tergo*; in other words, the action of the heart is either insufficient or is in some way hindered from exercising its full influence upon the blood in the capillaries and the veins. That the force of the heart's action is not deficient is proved by the high blood pressure present in all cases where it has been recorded.

	Pulse Rate.	Blood Pressure.
Saundby, Case II ...	80 ...	170-180
Parkes Weber, Case I ...	65 ...	140-170
Parkes Weber, Case II ...	80-90 ...	152-157
Hutchison and Miller ...	50-60 ...	130-145

This increase of the blood pressure can be attributed to vasomotor action, giving rise to spasm, and later on, through its persistence, to thickening of the middle-sized arteries. Of this thickening there is also a certain amount of *post-mortem* evidence. In Parkes Weber's first case he says all the medium-sized arteries seemed somewhat thickened, and the microscopical report says transverse sections of both right and left radial arteries seemed to show a decided relative increase in the size of the muscular coat, all due allowance being made for shrinkage during preparation of the specimens; Hutchison and Miller also found great thickening of the adventitia of the arterioles of the heart's walls. But there is a good deal of further clinical evidence of vasomotor disturbance; in the first place there is the universal redness of the skin, and it is of some importance to bear in mind that the appearance is constantly described as rather florid or ruddy than cyanosed, and that the latter expression seems only to be used in the description of the later stages, or where cold or some other temporary cause still further increases the stagnation. In addition to this universal redness of the skin is the influence of position upon it, so that the dependent parts become sometimes absolutely purple, as in the description of H.'s condition (Case I), when he was admitted finally just before his death. The occurrence of erythromelalgia can hardly be regarded as simply a coincidence, for it has been noted by Parkes Weber, Cabot, Türk, Collins, and Weintraud, and this condition is generally admitted to depend upon vasomotor disturbance; also there is in G. Y.'s case well-marked dermatographism, another vasomotor phenomenon.

CONCLUSION.

It is right that I should try to formulate my own conclusion as to the nature of this disease. I have explained that I cannot accept the view that it is a primary disease of the bone marrow or of the spleen, or that sufficient changes have been met with in the hearts of these cases to make it reasonable to suppose that the defect lies there. I have adopted the view that the mechanism of the obstruction to the circulation is the narrowing of the middle-sized arteries and arterioles—a condition which originally is no doubt nervous and depending upon vasomotor spasm, but which, in course of time becomes organic from thickening of the muscular and fibrous coats. This vasomotor derangement is a neurosis associated with a general neurasthenic condition which certainly, in some cases, seems to have been caused by an attack of influenza. I think it will be admitted by every one who has carefully watched the results of the epidemics of influenza during the last seventeen years that the toxins of influenza are responsible for many disturbances as grave as this, and that in adding one more to the accusations against it its defenders cannot plead that it is either innocent of evil or incapable of producing as dire results. However, I by no means wish to limit myself to influenza as the only possible explanation of the origin of this disease. The toxins of many other infections may, under certain circumstances, be equally injurious; yet it may be noted that its history exactly coincides in time with that of the recent revival of epidemic influenza.

To summarize what has gone before, I may say that I

believe the condition to be a cerebro-spinal neurasthenia, causing vasomotor spasm, with engorgement of the capillary and venous circulation and congestion of the internal organs, especially of the liver and spleen, with muscular weakness, loss of knee-jerks, and mental impairment, shown by loss of memory, apathy, and drowsiness.

[I desire to express to my friend and colleague, Dr. James W. Russell, my thanks for assistance received by directing my attention to several papers I should otherwise have overlooked, and to place on record the fact that it is entirely due to him that the first case did not remain lost to sight among a mass of notes, for although I took a considerable interest in it at the time, I had not thought of publishing it and had forgotten it. I must also add my acknowledgement of the ingenuity, zeal, and ability shown by Dr. Mackey, the present Resident Medical Officer at the General Hospital, in carrying out the very large number of clinical observations that have been made in this case, the extent of which is imperfectly indicated in the brief summary I have read. I must also thank Mr. L. C. S. Broughton for several careful chemical and spectroscopic reports on the pigments present in the urine.]

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A CASE OF SPLENIC LEUKAEMIA COMPLICATED WITH GOUT AND ALBUMINURIA.

By GEORGE PARKER, M.D.,
PHYSICIAN, GENERAL HOSPITAL, BRISTOL.

INSTANCES of leukaemia with fulminating attacks of uratisis are sufficiently rare to justify an account of a well-marked case.

The patient, aged, 35, a fitter by trade, has been under treatment for eighteen months for splenic leukaemia with frequently-recurring joint troubles. In May, 1901, he was attacked by malaria while at a port in the United States. A year or two afterwards he was laid up suddenly with pains in the knee which came on after a heavy turn of night work. In January, 1905, he was admitted as an in-patient at the General Hospital, Bristol, with pyrexia, joint pains, marked anaemia and breathlessness. The big toe, ankle, and right knee were red, painful, and swollen, while the wrist, elbow, and fingers were also slightly affected. The urine was 1010, acid, and showed a trace of albumen, but no sugar. The retinal discs were normal. The spleen reached below the umbilicus, and a blood count showed red cells 2,610,000, white 223,200, and numerous myelocytes. There was a systolic murmur at the apex of the heart. The lungs were normal except for slight dullness at the bases. There was no tenderness over the sternum.

Under treatment by sodium cacodylate the red cells rose by March 21st to 3,260,000, the white fell to 71,000. The haemoglobin reached 48 per cent., but the myelocytes remained as high as 26 per cent. Treatment by the Roentgen rays was kindly undertaken by Dr. W. Kenneth Wills, and steady improvement followed. The spleen decreased in size, the blood became practically normal except that 3.2 per cent. of myelocytes were still present, and in June he resumed work, but came up for the x-ray treatment periodically till November. In February, 1906, he relapsed, and again came under treatment; the leucocytes now reached 134,000 and the myelocytes 27 per cent. By April the white cells had fallen to 33,000 and the myelocytes to 12 per cent. The spleen later on diminished and could no longer be felt below the ribs.

Frequent slight attacks of arthritis have occurred during all this time in various joints. There is no marked deformity, but slight creaking in the right knee and a deposit of urates along the extensor tendons of both index fingers near the proximal interphalangeal joints. One of these discharged for a time. In March a tophus found on the right ear was punctured. The contents proved to be sodium urate. After an inflammatory attack the joints show a fine desquamation. Colchicum, thymine acid, and other remedies have been employed, and appear to hasten the termination of an attack.

For some time there was reasonable doubt as to the nature of the arthritis. Garrod's serum test was tried unsuccessfully. The moderate pyrexia at first and the transference of attacks from joint to joint was in favour of true rheumatism. However, when uratic deposits were found the question was settled. He can give no history of gout in his family, and never suffered from serious illness before the malaria. As to the causation of the kidney trouble, he has no recollection of scarlatina as a child. As a fitter he has constantly used red and white lead in his work, but remembers no attack of colic, and his gums show no blue line. The heart is slightly enlarged, the apex $\frac{1}{2}$ in. external to the nipple line, the aortic second sound is accentuated, and there is a systolic murmur at the apex. The systolic blood pressure is 110 mm., and the vessels seem healthy. The liver dullness extends from the sixth rib to about a couple of inches below the costal margin.

The urine is clear, acid, has rarely any deposit, and has always shown a definite cloud of albumen. The quantity varies between 30 and 50 oz., and the specific gravity between

1010 and 1020; numerous granular and a few hyaline and fatty casts have been noted. No prolonged examination of the other constituents has been made, but I may give one report made during a period when the gout was quiescent:

"Quantity of urine 48 oz., urea 1.3 per cent., so that the total excreted was 272.8 grains of urea. The nitrogen represented by the purin bodies was found to be 0.0286 per cent., which gives 5.99 grains of purin nitrogen in twenty-four hours." During an attack the urea was 205 grains and the purin nitrogen 3.8 grains.

A severe inflammatory attack of gout occurred during May, 1906, when he had gone home to resume work; many joints were affected, and fresh uratic deposits appeared.

Blood Counts.

	Feb. 3, 1905.	Feb. 25, 1905.	March 21, 1905.	April 17, 1905.
Red cells ...	2,610,000	—	3,260,000	3,460,000
White cells ...	223,000	82,000	71,000	61,200
Polymorphonuclears ...	34.2	10	49	65
Myelocytes ...	25.2	79	30.4	15.8
Basophiles ...	16.6	—	10.2	4.4
Nucleated red cells ...	3.8	4.0	0.2	1.6
Haemoglobin ...	—	—	48	—

	June 7, 1905.	Sept. 12, 1905.	Sept. 19, 1905.
Red cells ...	4,850,000	3,540,000	3,750,000
White cells ...	20,000	67,000	44,800
Polymorphonuclears ...	77.8	—	—
Myelocytes ...	3.2	—	—
Basophiles ...	6.2	—	—
Nucleated red cells ...	—	—	—
Haemoglobin ...	60	—	52 per cent.

	Feb. 14, 1906.	Feb. 26, 1906.	March 3, 1906.	March 27, 1906.	April 10, 1906.
Red cells ...	3,220,000	2,310,000	3,040,000	3,400,000	3,310,000
White cells ...	134,000	116,000	108,000	140,000	63,000
Polymorphonuclears ...	51	44	532	48	66
Myelocytes ...	27	29	25	32	12
Basophiles ...	0.8	0.6	1.6	1.2	3
Nucleated red cells ...	—	—	—	—	—
Haemoglobin ...	50	40	55	55	60

The interest of the case depends largely on the importance we attach to the retention theory of gout. Garrod laid down that during acute gout uric acid exists in the blood in excess, and that very little appears then in the urine. As the attack passes off, it reappears in the urine, and sometimes in large amounts, but during the quiet intervals the excretion is deficient. This retention of uric acid by the kidneys forms an essential feature of gout. In leukaemia there is an excess of urates in the blood unequalled in any other condition except gout and temporary states such as pneumonia. Why then, it was asked, do we not get a deposit of urates and other symptoms of gout in leukaemia? Simply because the kidneys there are active, and the uric acid excretion is vigorous. The so-called quadriurates have not time to change into the gelatinous biurate, and this into the crystalline form. It is certainly curious that cases of gout combined with leukaemia are decidedly rare. I have only found three recorded—one mentioned by Roberts and two by Duckworth, but in two of the three gout had existed long before. Roberts says: "I am not aware that any case has been recorded in which gout supervened as a clear consequence and result of splenic leukaemia. In the present instance the evidence as to priority is not clear. The patient had first an attack of malaria, which is well known to be a precursor of leukaemia. Gowers, for instance, found a history of malaria in 20 per cent. A year later he was attacked by