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A Case of Chronic Polycythæmia with Enlarged Spleen, probably a Disease of the Bone-marrow.

By F. Parkes Weber, M.D., F.R.C.P., and J. H. Watson, M.B., B.S. *Read March* 11, 1904.

THE patient, Gerardus R., a cabinet-maker, æt. 58 years, a native of Holland, who since 1871 had lived in England, was admitted to the German Hospital at the end of November, 1903, complaining of vertigo and inability to do his work properly. He was then found by Dr. Weber to present the peculiar symptom-complex, chronic cyanosis with enlargement of the spleen, and polycythæmia. Following is the past history.*

He was said formerly always to have had a very ruddy complexion, but during the last six or seven years an increasing liability to blueness of the nose and extremities had been observed. He had always been subject to indigestion, constipation, headaches, and occasional insomnia. Five years ago he brought up some blood (? hæmatemesis), and attended as an out-patient at a London hospital, but had no recurrence. At one time he seems to have been treated for stricture. No history of any other illnesses was forthcoming. He had certainly always been strictly moderate in regard to alcohol, and was known to have had a great aversion to intemperance. Of late years he had been subject to giddiness and feelings of weakness in the knees. The giddiness often came on when he got up from a chair or bed, and when he was doing his work. It had prevented him from following his employment during the last year or so.

In the latter part of the summer of 1903 he fractured some ribs and was an in-patient from August 31 to September 23 at the German Hospital. After leaving the hospital he had some mental trouble (part of his possessions were apparently sold to pay his rent), and ideas of persecution were first noticed. When readmitted to the hospital on November 30 his manner was quite different to what it had been before. He had become extremely emotional. It was

* Some of it obtained from a daughter of the patient.

difficult to get him to eat, and he had delusions. On December 7 he had to be removed to an infirmary, and on December 11 was transferred to Colney Hatch Asylum.* His mental condition seemed to improve there at first, and he nearly lost his delusions, yet he remained bodily and mentally feeble. On the morning of February 4 marked increase of the cyanosis was noted, and he died suddenly from syncope in the evening.

Family history.—Father and mother lived to a fair age; the former is said to have died of "heart disease." Several brothers and sisters are living in Holland, and some or all of them are remarkably ruddy in the face. There is no family history of insanity. The patient had one son who died of consumption. Another was epileptic, and died at nineteen years of age. Two other sons and two daughters are living and healthy.

Clinical Features of the Case as observed at the German Hospital and Colney Hatch Asylum.

The patient was a well-proportioned man with fair muscular development, but rather thin. His weight in December, 1903, was 10 st. 3 lbs. His skin was dry, and he was always more or less cyanosed. His fingers were slightly clubbed.

The cyanosis.—This was specially marked over the nose, malar prominences, lips, ears, hands, and feet. It varied in degree considerably from time to time. It was markedly increased whenever the patient became mentally excited, and was extreme shortly before he died. A slight pigmentation of the skin of the face was probably a result of the chronic cyanosis.

The temperature was slightly subnormal.

Thoracic organs.—There was evidence of a moderate amount of pulmonary emphysema. The heart presented no obvious signs of disease. No murmur was heard on any occasion. The respirations averaged fifteen per minute, the pulse being generally about sixty-five per minute.

Circulatory system.—The radial arteries felt a little thickened. The pulse was regular, of average frequency (about 65), of medium volume, and generally of decided high tension. Sphygmographic tracings with a Dudgeon's instrument showed a pulse of sustained pressure, almost anacrotic in

* We must express our thanks to Dr. W. J. Seward, medical superintendent of the asylum, through whose kindness every facility was given us to make our observations.

character. By Hill and Barnard's pocket sphygmometer we estimated the blood pressure in the radial artery as equivalent to about 120 mm. mercury,* and on different occasions by their larger instrument on the arm we found it reached 140 to 170 mm. mercury. There were no varicose veins in the lower extremities, and no venous pulsation or distension at the root of the neck was observed. Dr. R. Gruber kindly made an ophthalmoscopic examination, and found nothing abnormal except extreme distension of the retinal veins and very minute vessels, some of the veins having a slightly moniliform appearance. Doubtless, chiefly owing to the distension with blood, many minute vessels were visible which in ordinary persons would be invisible.

The abdominal organs.—The *spleen* was certainly enlarged, and could easily be felt during inspiration below the costal margin. By palpation nothing else abnormal could be found. There was no distension. We thought that the liver was not enlarged.

The urine.—The average daily quantity of urine was estimated at about 40 ounces, whilst the patient was drinking about 55 ounces of fluid *per diem*. Dr. Watson estimated the urea in the urine at about 13·25 grains to the ounce, which would make a daily excretion of about 530 grains (34½ grammes)—that is to say, about the normal amount. The urine was of about specific gravity 1020, usually clear, acid, free from sugar, but yielding a cloud of albumen (about 0·5 per mille by Esbach's tube). It was of a deep orange colour, and on dilution showed a urobilin absorption band by spectroscopic examination. Heating with a little nitric acid heightened the colour. The addition of a perchloride of iron solution caused a reddish-brown colour reaction. No urinary casts were detected by the use of the centrifugal machine and microscopic examination. Following is a report on a specimen of the patient's urine kindly written out for us by Dr. A. E. Garrod:

"The urine contained a large amount of uro-erythin, and threw down a deep pink urate sediment. The filtrate showed a very pronounced urobilin band, the amount of urobilin being obviously considerably in excess. The filtrate was rendered acid with acetic acid, and was then shaken with some amylic alcohol. The amylic extract showed a dark uro-

* That is the pressure at which the *maximum pulse oscillations* were shown by this instrument, not the pressure sufficient to suppress the oscillations.

bilin band and very faint bands of hæmatoporphyrin, indicating an amount of that pigment rather above the normal trace, but only such as is often seen in morbid urines. The presence of this last pigment in such amounts has no special significance. The pigmentation of the urine was such as is often seen when there is either organic disease or functional derangement of the liver."

The blood.—At the beginning of December, 1903, when the patient was at the German Hospital, the hæmoglobin value of his blood from finger and ear, was estimated (Dr. Campiche at the request of Dr. Weber) at about 150—160 per cent. of the normal. Red cells about 9,000,000 per c.mm., white cells about 12,000. No abnormal blood-cells were seen. At Colney Hatch Asylum we were able, after saturating the blood with coal-gas, to carefully estimate the hæmoglobin value by using Haldane's modification of Gowers' hæmoglobinometer. Though this instrument is graduated to measure only up to 130 per cent., the divisions of the scale are at equal intervals from each other, and so we were able to calculate that the hæmoglobin value in our patient was approximately 170 per cent. Four blood-counts were made on different occasions at Colney Hatch and the red corpuscles were estimated at between ten millions to slightly over eleven millions, and the white cells at between 7,500 and 8,000 per cubic millimetre. On January 17, 1904, the red cells were put down as 10,700,000, the white cells as 8,000. The white cells were not counted at the last examination, namely on January 29, when the number of red cells reached 11,150,000. Blood-films of January 31 were searched for erythroblasts, but with a negative result. A differential count of white cells was made by Dr. G. L. Eastes (December 21, 1903). Of 400 white cells counted he found that the small lymphocytes made up 13·2 per cent., the large lymphocytes 4·2 per cent. (total lymphocytes 17·4 per cent.), polymorphonuclears 82·4 per cent., and coarsely granular eosinophile cells 0·2 per cent. Dr. Eastes added that during the count no myelocytes or other abnormal cells were seen, and there was no poikilocytosis. The average diameter of the red blood cells (Dr. Watson by Ramsden's micrometer eye piece) was found to be 7·1 micro-millimetres (measured in dried films), that is, if anything, slightly below the average. On a glass microscope slide * the coagulation time of the blood (that is, for the beginning of coagulation),

* *Vide* the clinical method recommended by Dr. M. Copeman in Allbutt's *System of Medicine*, vol. v, p. 451.

was found to be one and a half to two minutes. We endeavoured by Hammerschlag's and by another method to estimate the specific gravity of the blood and made it slightly over 1060, but we may have underestimated it.

The Nervous System and Mental Symptoms.—Nothing abnormal was found on examining the patient's pupillary reactions, knee jerks, or other reflexes. No motor paresis, incoordination or abnormality of sensation was to be found. The muscular sense was normal. The speech was not affected, except that it was rather slow, perhaps owing to mental confusion. We need not add anything to what we have already said in regard to the headaches, the vertigo, and the feelings of giving way of the knees and prostration, to which the patient was subject. The following *résumé* (Dr. Watson, January 24, 1904) of his mental symptoms at Colney Hatch Asylum shows that the state of his mind was one of "confusional insanity:"

"The patient is very talkative, very confused, and more or less incoherent; his sentences are very disjointed. He seems not to know where he is. He is slow in understanding what is said to him. He behaves himself fairly well, and is not violent or destructive, but rather slovenly in his dress; in his habits he is quite clean. Since admission he has taken little or no interest in his surroundings. As a general rule he sits moping in front of the fire, and has to be literally dragged away to his meals. At the table he plays with his food, eating very slowly, and apparently with no relish. After meals there is the same difficulty in getting him to leave his seat. His mood is changeable, but for the most part depressed. His moral conceptions and judgments are quite natural. His memory is much impaired both for past and recent events. He does not mistake objects (apraxia). At present there is no evidence of illusions or hallucinations. Delusions are not marked, but at times evident, and of a depressive type. At one time he was convinced that his food was poisoned. He has no suicidal tendency."

Necropsy (Dr. Weber).

To avoid repetition we will say at once that one of the most remarkable appearances noted was the extreme distension of all the minute venules with blood. This was especially striking when the abdomen was opened. The minute mesenteric venules reminded one of the appearance seen in

an anatomical preparation in which the vessels had been very forcibly injected with some dark bluish "mass."* This corresponds to the state of things found in a similar case by Türk (see *Literature* at the end) and likewise exactly corresponds to Dr. Gruber's description of the fundus oculi during life (to which we have already alluded). We may also here mention that all the viscera were hyperæmic. In fact, as a histological examination of the various organs subsequently showed, the microscopic blood channels were engorged with blood just as were the minute venules which could be seen with the naked eye. All the medium-sized arteries (radials, basal arteries of the brain) seemed somewhat thickened.

Brain and skull.†—On the inner surface of the calvarium the vascular grooves are peculiarly well-marked, in fact, more of these channels are seen than in ordinary skulls. This doubtless corresponds to the distension of small and medium-sized veins all over the body, to which we have already referred. There is slight thickening of the pia-arachnoid, which is intensely congested. The membranes strip easily and leave no erosion. No gross lesion can be found in the brain. The cortex is unduly dark, evidently due to the vascular engorgement and dark colour of the blood. Weights: Whole brain, 1460 g. = $51\frac{1}{2}$ ounces; right cerebrum, 640 g. = $22\frac{3}{5}$ ounces; left cerebrum, 635 g. = $22\frac{2}{5}$ ounces; cerebellum, pons and medulla, 190 g. = $6\frac{7}{10}$ ounces; right cerebrum, after stripping off membranes, 610 g. = $21\frac{1}{2}$ ounces. The pituitary body is not enlarged.

Lungs.—Large and moderately emphysematous, somewhat unduly covering the anterior surface of the heart. There are a few small hæmorrhagic infarcts (? thrombotic or embolic) in the anterior edge of the lower part of the right lung, and one at the base of the left lung. Both lungs engorged with blood. No evidence found of old or recent tubercle, except a little pleuritic puckering from slight former disease at both apices. No pleuritic adhesions, but a few small flakes of recent lymph are present at the left pulmonary base. Weight of both lungs together 1300 g. (46 ounces).

Heart.—Of medium size, but showing a decided relative

* It must be remembered, however, that the distinctness of all the small veins was doubtless due not only to their distension, but also to the high hæmoglobin value and the venosity of the blood they contained.

† Kind assistance was given by Dr. C. F. Beadles at the necropsy, especially in the examination of the brain.

hypertrophy of the left ventricle. Weight about 298 g. (10½ ounces).* Both ventricles firmly contracted.† The mitral orifice admits two, the tricuspid orifice three fingers. The two anterior curtains of the aortic orifice are partly united by an old, hardish vegetation (of the size of a medium pea) situated between them, but excepting slight thickening of the mitral cusps there is no other valvular disease. No aperture in the interventricular or interauricular septa. No congenital disease. The ductus arteriosus is represented by a thin tendinous cord. There is some slight atheromatous change in the thoracic aorta. There is a little (possibly *ante-mortem*) colourless clot rather firmly fixed in the meshwork of muscular trabeculæ of the right auricular appendix. We may here point out that the weight of the heart and the absence of any murmur during life prove that the mechanism of the aortic valves cannot have been much impaired by the old slight disease found at the necropsy.

Spleen.—Uniformly enlarged. Weight 655 g. (23 ounces). A few small perisplenic adhesions. There is one tough, whitish, depressed wedge-shaped scar on the convex side of the spleen, doubtless representing an old infarct. On section the splenic substance appears normal to the naked eye. There is no disease in the splenic arteries and veins.

Liver.—Weight 1760 g. (62 ounces). No evidence of disease. No nutmeggy appearance on section.

Kidneys.—Weight of both together 445 g. (16 ounces). Capsule strips fairly easily. Cortex not noticeably diminished. The substance of both these organs is rather hard.

The *supra-renal capsules* appear macroscopically not to be diseased‡; and nothing unusual is observed in examining the *urinary bladder* and *testes* beyond *varicocele.*

The alimentary canal.—The mucous membrane of the stomach is intensely congested. A round ulcer, with sharp

* This weight was taken only after the heart had been lying for a considerable time in weak formalin, but the weight of the spleen which had been lying with it was found to have hardly altered at all.

† Albanese, in his experiments on the hearts of frogs, found that if the circulating fluid was not viscid enough the heart's action was arrested in diastole. In conditions of polycythæmia, as we shall subsequently point out, the blood is too viscid (*Arch. f. exp. Path. u. Pharm.*, Leipzig, 1893, vol. xxxii, p. 296).

‡ In regard to the occurrence of hypertrophy of the supra-renals in connection with changes in the blood-vessels (*vide* Gouget, Société de Biologie, Paris, December 19, 1903; and O. Josué, *Presse Médicale*, Paris, May 4, 1904, p. 281; and Aubertin and Ambert, *Tribune Médicale*, Paris, 1904, p. 119), we are sorry that we omitted to take the weight of these organs.

edges, of the diameter of a shilling, is situated on the posterior surface about two inches away from the pylorus. At the site of the ulcer there are old peritoneal adhesions between the stomach and the adjacent parts. The lymphatic follicles of the mucous membrane of the ileum near the ileo-cæcal valve appear somewhat enlarged, but otherwise there is no intestinal disease. Some "coffee ground" material is noted on opening the stomach and intestine (? from the gastric ulcer or congestion of the gastric mucous membrane).

The mesenteric glands are moderately enlarged. No big hæmolymph glands are to be found near the aorta.

A few atheromatous patches are present in the lower part of the *abdominal aorta.*

The *thyroid gland* weighs 35 g. ($1\frac{1}{5}$ ounce) and appears normal to the naked eye.

Bones and joints.—The left humerus, sawn through longitudinally, shows red transformation of the marrow of the whole of the shaft. The left femur and the right tibia, both sawn through transversely in the centres of their shafts, show bone-marrow of the same deep red appearance. Transverse section through the shafts of smaller long bones, namely the right fibula, the right radius and the right ulna, shows relatively pale and fatty-looking marrow. The cancellous tissue of the sternum is very red. On examination of one of the large joints (left shoulder joint) nothing abnormal can be found.*

Microscopical Examination.

An account of the examination of the blood has already been given.

The *bone-marrow.*—Sections of bone-marrow from the shaft of the left humerus were stained (1) by hæmatoxylin and eosin, (2) by methylene blue and eosin, (3) by polychromic methylene blue, (4) by Jenner's blood-stain, (5) by Leishman's blood-stain, (6) by Ehrlich's triacid stain, (7) by Mann's biacid methyl-blue and eosin mixture (*vide* Mann's description of his longer method in his *Physiological Histology*, 1902, p. 216), (8) by carbol-fuchsine and methylene blue.

The tissue was found to consist of nucleated cells and thin-walled vessels distended with blood.

* We have to thank Dr. F. W. Mott, F.R.S., Pathologist to the London County Asylums, for his kind interest and the loan of several instruments. He was prevented by illness from being present at the *post-mortem* examination.

The fat cells, of which normal marrow from the shafts of long bones chiefly consists, were represented only by a vesicle here and there. Four classes of nucleated cells could be distinguished—

(A) The greater portion (*i. e.* greater in bulk if not in actual number) were rounded or polygonal cells, containing a rather large vesicular nucleus with scanty chromatin network surrounded by a good deal of faintly-stained protoplasm gener-

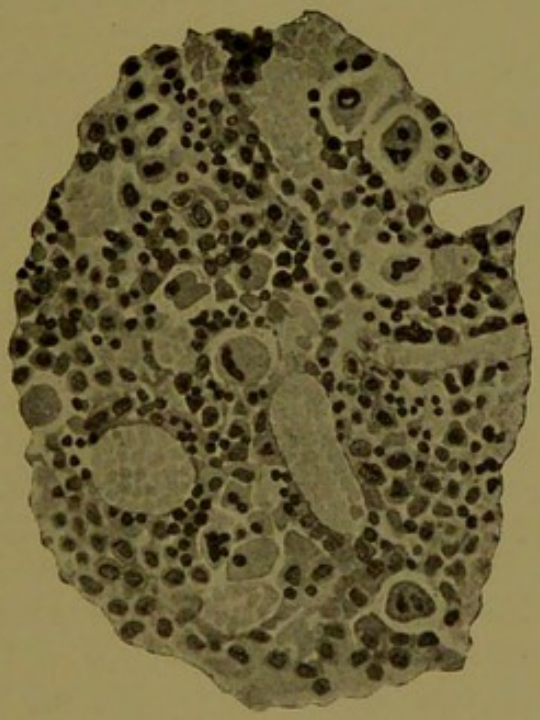

FIG. 1.—Microscopic section (hæmatoxylin) of the bone marrow from the shaft of the left humerus (× 220). It shows a tissue consisting of myelocytes, erythroblasts, and giant-cells, together with thin-walled dilated blood-vessels full of red blood corpuscles. There are no fat vesicles visible. The erythroblasts are distinguished in this specimen by their small dark nuclei. Most of the other nucleated cells are myelocytes (the eosinophile myelocytes are not specially stained in this specimen). There are several giant-cells present.

ally without distinct granules. Although we seldom saw any distinct granules in these cells, we regard them as "representing" the ordinary neutrophile myelocytes. We have, however, no objection to calling them, at least those which showed no distinct granulation, "mononuclear cells of the large lymphocyte type," for we believe that cells of the large lymphocyte type, when they occur in the bone-marrow, should be generally regarded as "non-granulated myelocytes." Certain cells, which apparently belonged to the same group,

were smaller, had little protoplasm around their nuclei, and reminded us of ordinary lymphocytes.

(B) Scattered about throughout the sections were a fair number of cells somewhat resembling class A, but their nuclei were often smaller and more deeply stained, and were sometimes lobed or otherwise irregular in form, and their cytoplasm contained eosinophile granules. These we regarded as eosinophile myelocytes, although their granulation appeared less coarse than that of typical coarsely-granular eosinophile cells.

(C) Almost as numerous as the cells of group A, and in some parts of the sections more numerous, were cells having a nucleus staining very deeply (at least with hæmatoxylin and with methylene blue) and quite or almost homogeneously. In these cells the amount of cytoplasm around the nucleus varied considerably, but most of the nuclei seemed to be surrounded by a thin film only. Moreover there were a great many nuclei apparently without any cytoplasm around them. Chiefly on account of the intense staining of their nuclei we regarded these cells as erythroblasts, though their cytoplasm with most of our stains took on a different colour to that taken on by the erythrocytes. The cells and also their nuclei were not all of the same size, but by far the majority might be classed as normoblasts or the nuclei of normoblasts. Sometimes two or more nuclei were seen in the same cell, and sometimes the nucleus appeared rosette-like or irregularly split up. These cells were very unevenly distributed through the sections, occurring scattered about in some parts, but in other parts collected together in clumps. Their nuclei, notably the nuclei without any protoplasm around them, were generally deeply tinted by the eosin in sections stained by Mann's eosin-methyl-blue method.*

(D) A good number of large endothelioid cells and typical giant-cells were present scattered about over all parts of the sections.

For certain reasons, into which we need not enter, a search for tubercle bacilli in the bone-marrow was made, but with negative results.

The spleen.—The Malpighian corpuscles appeared normal. The enlargement of the organ seemed to be due merely to increase of the splenic pulp and engorgement with blood.

Sections of an enlarged *mesenteric lymph-gland* from near

* Possibly owing to some necrobiotic change having occurred.

the stomach showed considerable increase of the fibrous tissue of the trabeculæ, apparently the result of chronic adenitis. Considering that the patient had a chronic ulcer of the stomach this evidence of chronic inflammation in a neighbouring lymph-gland was not surprising.

In sections of the *liver* nothing remarkable was seen beyond engorgement of the organ with blood and a certain amount of deposit of brown pigment granules in the central portions of the acini. Although this pigment deposit is similar to that which is ordinarily seen in chronic venous congestion of the organ, there was evidently no near approach to the condition of "nutmeg liver." By the potassium ferrocyanide and hydrochloric acid method no evidence of the presence of free iron was obtained in sections of the liver and spleen.

Microscopical examination of a *kidney* showed no interstitial nephritis, and certain parenchymatous changes in the renal epithelium were probably of *post-mortem* origin. A feature worth mentioning was the remarkable engorgement of the minute renal blood-vessels. In fact, in sections counterstained with eosin the appearance due to the vascular engorgement was similar to that in sections of a kidney the vessels of which had been forcibly injected with a bright red material for demonstration purposes.

Transverse sections of both right and left *radial arteries* seemed to show a decided relative increase in the size of the muscular coat ("arterial hypermyotrophy"), all due allowance being made for shrinkage during preparation of the specimens. This confirmed our previous conclusions as to thickening of the medium-sized arteries generally.*

Remarks.

It is quite clear that the foregoing case is an example of the clinical group described under the heading "Polycythæmia with Splenomegaly and Chronic Cyanosis," or under some similar heading, by several different observers, and in the English language, notably by Osler (see *Literature* at the end).† We must here shortly recapitulate the main points.

* We have to thank Mr. S. G. Shattock for his kindness in looking through sections of some of the viscera with us.

† Perhaps cases of chronic cyanosis with enlarged spleen and polycythæmia in which the splenomegaly was found to be due to tuberculosis (as in the case of Rendu and Widal) should be placed in a separate group. In acute tuberculosis of the spleen (as in D. D. Stewart's case) polycythæmia may be absent, possibly because the disease has not lasted long enough.

The patient was a man æt. 58 years, who had always been very ruddy in the face, though strictly temperate with regard to alcohol. He had apparently usually enjoyed fair general health, though always inclined to "indigestion" and constipation. A tendency to blueness of the nose and extremities had been noticed during the last six or seven years. Latterly he had been subject to feelings of giddiness and prostration, which prevented him from following his employment.

At the end of 1903, some time after an injury (fracture of ribs), he began to suffer from delusions, and had to be admitted to a lunatic asylum, where, in spite of apparent mental improvement, he seemed to get weaker. He died suddenly of syncope during a period of increased cyanosis.

The *post-mortem* examination showed the presence of a certain amount of pulmonary emphysema, and slight old disease at the aortic orifice of the heart, but these changes were quite insufficient to account for the enlarged spleen, and for the polycythæmia,* and the other symptoms observed during the patient's life. Moreover, the liver had not the typical "nutmeg" appearance of chronic passive congestion as it would have had if the enlargement of the spleen had been due to pulmonary emphysema and cardiac disease. On the other hand, the examination of the patient's bones showed that almost all the ordinary yellow (normal) marrow of the shafts of the long bones was in this patient replaced by red marrow, from which fat cells were nearly absent, in other words, the amount of erythrocyte-forming tissue in this man's body was immensely greater than in the bodies of ordinary persons. It became, therefore, obvious that even if the formation of red blood-corpuscles had not been particularly active in any one part of the bone-marrow, the total production of red cells in the patient's body must have been much above the average, owing to the great excess of the tissues engaged in manufacturing them. In this connection it may be noted that in Cabot's second case, and in two of Türk's cases, erythroblasts were found during life in the circulating blood, indicating increased activity of the erythrocyte-forming functions of the bone-marrow (see *Literature* at the end). In regard to destruction of red cells, we have no

* Contrary to the statements of some writers it seems that in chronic cyanosis due to heart disease the red corpuscles may exceed seven or eight millions per cubic millimetre. Thus, in a seven-year-old girl with congenital pulmonary stenosis Friedel Pick (*Verein deutscher Aerzte in Prag*, January 22, 1904) recently found the erythrocytes to be over ten millions per cubic millimetre.

certain evidence in our case that this was increased, though judging by the enlargement of the spleen,* the high colour of the urine, etc., it is more likely to have been increased than diminished.

We repeat, then, that in the present case we have abundant evidence that an increased production of erythrocytes was taking place in the bone-marrow, and in Saundby and Russell's case, though it is stated that the marrow of the femur was normal on naked eye inspection, no microscopic examination was made, and the marrow of other bones seems not to have been examined. It must be remembered, however, that as yet there have been only very few necropsies on cases of this class, and in scarcely any of them has the bone-marrow been examined.

The question arises, What was the cause of the bone-marrow changes in our case? We must acknowledge that such changes may probably sometimes be secondary to circulatory disturbance from heart disease. Thus, in *post-mortem* examinations on two children with congenital pulmonary stenosis and cyanosis, E. Weil † found that there was red transformation of the bone-marrow, sections of which showed that all traces of the normal fatty tissue had disappeared. In our case and similar cases, unlike such "cardiac" cases, we would provisionally regard the changes in the bone-marrow as *primary*, or, if not strictly speaking primary, as representing an *excessive "vital reaction"* to stimulating agents which in ordinary individuals would have hardly been sufficient to excite any reaction at all.‡

Further than this we cannot go with certainty, but it has occurred to us that on one supposition we can account for

* In the cases of persistent cyanosis accompanying chronic tuberculous splenomegaly (case of Rendu and Widal, etc.), it seems possible that the polycythæmia may be partly due to diminished destruction of red cells in the spleen.

† *Soc. de Biologie*, Paris, June 29, 1901, p. 713.

‡ Dr. G. A. Gibson (*Lancet*, 1903, vol. ii, p. 1564) regards the whole symptom-complex as probably due to myocardiac weakness. We of course admit that polycythæmia may occur as a "vital reaction" resulting from imperfect oxidation of the tissues in cardiac disease, etc. If, however, the symptom-complex were in our class of cases really a "vital reaction" of this nature, it would appear to be a vital reaction out of all proportion to the exciting agents. We should therefore be driven to the assumption that the bone-marrow in these patients possessed the (congenital?) peculiarity of altogether excessive reaction towards any exciting agent, or, at least, to any stimulation of its erythrocyte-forming functions. In this connection it may be borne in mind that our patient had formerly always been distinguished by a very ruddy complexion, and that he belonged to a family with similar ruddy complexions.

the association of the chief phenomena constituting the symptom-complex of our own and similar cases. This supposition is that the osmotic tension of the blood of patients with extreme polycythæmia (whether as a result of the polycythæmia * or not) is higher than that of ordinary blood. Although there are many apparent physical objections to this supposition we have determined provisionally to entertain it, for it is only by this means that we can in any way explain the condition of patients of this group.

Further observations on similar cases will show whether our supposition is justified or not. At present we will endeavour to explain the main symptoms on the basis of our supposition. Granting it to be correct, it follows by the laws of osmosis that the blood contained in the vessels tends to give less fluid up to the tissues than normal blood. As a result of this, the small blood-vessels will be habitually distended † and there will be a true condition of "polyhæmia" or blood plethora ‡ as well as of polycythæmia. The spleen will become enlarged, since in a sense it is an elastic reservoir of blood at a pressure approximately that of blood in the capillaries, and, apart from enlargements due to structural diseases, varies in size mainly § according to the pressure of the blood within it.

In spite of the existence of true plethora in the vessels there would, according to the explanation we have proposed, be a tendency for the tissues to be imperfectly supplied with fluid from the capillaries, and consequently to be imperfectly

* However, a rough experiment made by Dr. Weber, with Dr. Lazarus-Barlow's kind assistance by means of his osmometer tubes, seems to show that artificial increase of the proportion of corpuscles in fresh horse's blood (coagulation prevented by the addition of ½ per cent. potassium citrate) rather lowers than raises osmotic tension.

† As we have subsequently shown, the viscosity of the blood is necessarily increased when there is polycythæmia. Hence we must acknowledge that the dilatation of the minute blood-vessels may be equally well explained as being *compensatory* to the increased difficulty in the circulation resulting from the abnormally viscous state of the blood.

‡ In spite of Cohnheim's classical teaching as to the great improbability or impossibility of any persistent true blood plethora (*vide* Cohnheim's *Lectures on General Pathology*, New Sydenham Society's translation, London, 1889, vol. i, p. 424).

§ From this point of view the spleen may be said to act as a manometer of the capillary blood-pressure. In regard to the present question one need not take into consideration the slight rhythmical variations in the volume of the spleen which have been studied by physiologists in animals, and which are doubtless due to the action of the unstriped muscular tissue in the trabeculæ and walls of the blood-vessels and capsule of this organ.

supplied with nutrient material, and with oxygen for combustion. Under such conditions, therefore, the skin and other tissues (in spite of the polyhæmia) would tend to be abnormally dry and rather ill nourished than well nourished, whilst metabolism would tend to be defective.

Similarly, secretions and excretions of the body would tend to be diminished. The daily output of urine would be below the average, and the urine itself probably more highly coloured. The gastro-intestinal secretions would be lessened and thus conditions of chronic constipation and dyspepsia would be favoured. The central nervous system, like the other tissues, would share in the nutritional disturbances, and feelings of prostration, headache, giddiness, and other symptoms might be complained of.

The presence of true plethora, as well as of increased viscosity of the blood (see later section), would tend to throw extra work upon the muscular tissue of the circulatory system and lead to hypertrophy (hypermyotrophy) of the arterial walls and left ventricle.

According to our hypothesis, as we have briefly explained, the vertigo and other nervous symptoms, as well as the scantiness of the urine, the dryness of the skin, the splenomegaly, and the distention of the minute blood-vessels as seen by the ophthalmoscope during life, would all be secondary to the osmotic state of the blood. The cyanosis of the face, ears, hands, and feet, which varies very much in degree at different times, and is apparently apt to be much increased by mental excitement and during attacks of prostration, may perhaps be partly explained as an expression of embarrassment resulting from excessive work thrown on the circulatory organs. It seems to us, however, that, according to our hypothesis, it would also be partly due to the osmotic conditions, if these were caused by the polycythæmia; in fact, we suppose that, granting the existence of such osmotic conditions, there would be an increased tendency for carbonic acid to be carried into the blood-vessels and a diminished tendency for oxygen to be carried from the blood to the tissues in patients of our class of cases as compared to ordinary persons.

Here we must make a short digression in regard to what in a preceding paragraph we said on *increased viscosity of blood*. We have succeeded in experimentally proving that, other conditions being similar, increase in the proportion of corpuscles to blood-plasma does decidedly increase friction in the flow of blood through capillary channels; that is to

say, it raises the "viscosity" of the blood. Professor J. McFadyean kindly provided us with a glass vessel containing 1000 c.c. of fresh horse's blood, in which clotting had been prevented by the addition of 10 grammes of a 50 per cent. aqueous solution of citrate of potassium. The corpuscles were given time to sink to the bottom of the vessel until two distinct strata were formed, a lower opaque red one containing almost only blood-corpuscles and an upper clear yellow one consisting of blood-plasma. It was then easy, by the help of a pipette, to obtain samples suitable for our purpose as follows: (1) a sample of the stratum of blood-plasma (of specific gravity 1025); (2) a sample of the corpuscular stratum; (3) a sample obtained by mixing one part of the corpuscular stratum with three parts of the plasma, the specific gravity of the mixture being about 1040; (4) a sample obtained by mixing one part of the corpuscular stratum with seven of the plasma, the specific gravity being about 1030. By means of a Thoma-Zeiss hæmocytometer it was found that the proportion of red cells in the first mixture (that is No. 3) was four millions per cubic millimetre; therefore the proportion in the other mixture (No. 4) was about two millions to the c,mm.* The four different samples were then compared in regard to viscosity by allowing them to run through a long glass capillary tube (similar to the tubing employed in the stems of thermometers) with a bulb in the upper part (for the pattern for which we are indebted to the kindness of Prof. A. Schuster, F.R.S., of Manchester), the time taken by the upper surface of the liquid to pass from a mark on the glass tube above the bulb to another mark below the bulb being carefully noted in each case. Distilled water took 43 seconds. The blood-plasma (No. 1) took 65½ seconds. The second mixture (No. 4) took 84 seconds. The first mixture (No. 3) took 110 seconds. We did not stop to ascertain the exact time taken by the sample of the corpuscular stratum (No. 2), because it evidently would have taken half-an-hour or longer. The temperature was constant during these experiments, and as the specific gravities of the different fluids were obtainable it would have been possible, as Prof. Schuster† pointed out,

* Professor McFadyean kindly informs us that the normal proportion of red corpuscles in horse's blood is usually given as 7 to 8 millions per cubic millimetre, and that their average diameter is 6 to 7 micro-millimetres (*i. e.* slightly less than that of human red corpuscles).

† He told us that if the time taken in two different liquids be t_1 and t, respectively, and p_1 and p_2 be the respective densities of the two liquids, and

to ascertain the coefficient of viscosity of each sample. All we required was, however, to prove, as we succeeded in

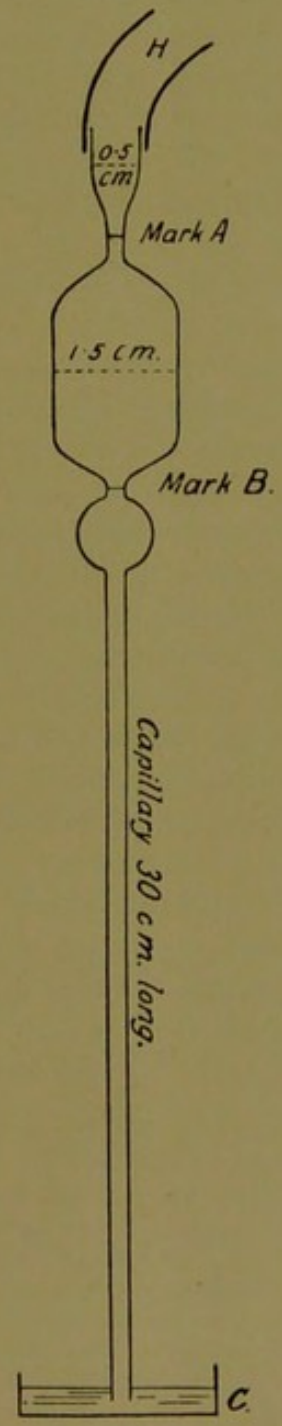

FIG. 2.—The liquid is sucked up from an open vessel, C, by means of an india-rubber tube, H. The liquid is then allowed to fall whilst the tube is kept in a vertical position. The times at which the upper surface of the liquid passes the marks A and B are noted.

n_1 and n_2 their coefficients of viscosity, then $\frac{n_1}{n_2} = \frac{t_1 p_1}{t_2 p_2}$; so that, if for one liquid (as in our case, for water), n_2 is known, n_1 may be calculated out.

doing, that increase of the corpuscular elements was accompanied by a decided rise in the viscosity of the blood.*

It is impossible to say in our case, as in other cases of the same group, precisely when the disease commenced. All we can state is that the cyanosis was noticeable during the last six or seven years of the patient's life. We have good authority for supposing that even before this time he had a markedly ruddy complexion, and that some of his near relatives were like him in this respect. Unfortunately we have not been able to examine the blood of these relatives, as they are not living in England.

Concerning treatment we have very little to suggest. It seems to us, however, that probably one of the most unfortunate things that can happen to a patient is to suffer from any accident temporarily preventing him from taking his usual exercise and the usual amount of fresh air, since deficiency of fresh air and want of exercise must almost certainly lead to diminished destruction of red blood-corpuscles. It is possible that in our patient the diminution of open-air exercise consequent upon the accident and the mental disorder may have had some influence in hastening the end. Injury to bones, such as occurred in our case, might perhaps aggravate the disease (1) by exciting the bone-marrow to increased activity; (2) by rendering rest indoors necessary, and thus diminishing the destruction of red blood-corpuscles.†

Venesection does not seem, according to our views, to be likely to do any good, unless in association with the introduction of normal saline solution to dilute the circulating blood. Such patients ought probably to be supplied with as great

* It follows that conditions of polycythæmia and oligocythæmia (whether absolute or relative) have some importance in regard to indications for venesection and for injections of normal salt solution (subcutaneous or intravenous). When we made these experiments we did not know of those of Jacoby, an abstract of which is given in the *Deut. Med. Wochenschrift* for February 21, 1901. By employing leech extract, or else by defibrinating blood to prevent coagulation, and by the aid of the centrifugal machine, he was able to study the influence of the proportion of corpuscles on the viscosity of the blood. He found that the viscosity was far more influenced by the proportion of corpuscles than by gummy (viscous) substances in the blood-plasma, and still more so than by the amount of salts, etc., present. By increase of corpuscles the viscosity of the blood was raised, and the excretion of urine slightly diminished, though the blood-pressure became slightly higher and the pulse-frequency remained the same. The bearing of Jacoby's experiments on the explanation of the present case is obvious.

† In this connection it may also be remembered that the patient suffered from a hæmorrhage (? from the stomach) five years before his death, and that any severe hæmorrhage may be regarded as a possible exciting or aggravating factor in the ætiology of bone-marrow diseases.

abundance of fresh air as patients suffering from pulmonary tuberculosis. Any food or drug such as iron-containing medicines,* known specially to excite the erythrocyte-forming functions of the bone-marrow, or coal tar products, such as acetanilide ("antifebrin"), known to cause cyanosis,† should, of course, be specially avoided.

Addendum (June, 1904).

If, as H. Ribbert believes (*Centralblatt für allg. Pathologie*, Jena, 1904, vol. xv, No. 9), there is a form of "myeloma," that is to say, of growth originating in the bone marrow, which should be termed "erythroblastoma," because the tumour-cells are allied to erythroblasts (*i. e.* derived from the embryonal ancestors of erythroblasts), it seems to us not unlikely that cases of *polycythæmia with splenomegaly*, such as our case, bear a relation to cases of erythroblastoma similar to that which the various forms of leukæmia bear to the various forms of "myelogenic pseudoleukæmia," that is to say, to the other (non-erythroblastic) forms of myeloma. (Cf. F. P. Weber, "A Case of Acute Leukæmia, with a Scheme of Classification of Leukæmias and Pseudo-Leukæmias," *Trans. Path. Soc. London*, 1903, vol. liv, p. 286.)

Literature.

(We have included references to some cases of enlargement of the spleen due to tuberculosis, in which chronic cyanosis constituted a prominent clinical feature.)

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* We regret that after the patient's death a quantitative estimation of the iron in the blood and various tissues was not undertaken.

† Osler (*Brit. Med. Journ.*, Jan. 16, 1904, p. 121) refers to a woman sent to him by Dr. W. P. Platt, with obscure cyanosis of two years' duration, but without enlargement of the spleen or polycythæmia. It was ascertained that she had been in the habit of taking a quack medicine containing acetanilide. In Stengel and White's case of chronic acetanilide poisoning there was great cyanosis, and the spleen could be felt two inches below the ribs. In spite of the cyanosis the number of red blood cells did not exceed three millions per cubic millimeter, but the relative abundance of erythroblasts was remarkable. It seems to us, therefore, that in such cases of chronic acetanilide poisoning increased destruction of erythrocytes accompanies increased production. It may here be noted that chronic carbon monoxide poisoning may lead to polycythæmia with relative or absolute hæmoglobin deficiency (von Jaksch in Nothnagel's *Handbuch der spec. Path. und Ther.*, vol. i, p. 257, and G. Reinhold in *Muenchener med. Wochenschr.*, 1904, No. 17, p. 739).

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E. Weil, "Note sur les organes hématopoiétiques et l'hématopoièse dans la cyanose congenitale," *Société de Biologie*, Paris, June 29, 1901, p. 713.

Case of Polycythæmia with Enlarged Spleen and Chronic Erythromelalgia of the Left Foot. By F. Parkes Weber, M.D., *Exhibited April* 22, 1904.

THE patient, Mrs. Sabina R., æt. 36, a Jewess from Roumania, has been under observation for a considerable time on account of erythromelalgia (see description in the *British Journal of Dermatology*, February, 1904, p. 70), but the presence of polycythæmia with splenomegaly has only recently been recognised. She came to England ten years ago, and up to that time had enjoyed fair health. She never had malaria. Both her parents reached old age. Her husband, a traveller, is living and healthy, and she has two children, both living and healthy, aged seven years and nine years respectively. Before these children she had two abortions at the third month. After her last confinement (seven years ago) she suffered from "inflammation of the womb," and the whole of her left lower extremity was swollen for a month.

Three or four years ago she commenced to have "burning" in both feet during summer, and gradually she became unable to put on her boots without pain. For the last two years she has suffered much from headache and feelings of giddiness and prostration. On account of the foot trouble she has been practically confined to bed for eighteen months. When Dr. Weber first saw her in the summer of 1903 her feet were turgid with blood (some of the toes were purple), painful, hyperæsthetic, hyperalgesic, and moist with sweat. All the signs were much more marked in the left foot, which was objectively the hotter of the two. Considerable improvement occurred, but the left foot has not completely recovered. At the present time the erythromelalgia is practically limited to the left foot. Even when the patient is lying down and resting one can always observe livid patches of skin, which are sometimes apparently slightly swollen, on the big toe and along the inner border of the foot, and this region is tender to pressure; but when she sits up with the feet in a dependent position the whole left big toe becomes blue and painful and hot to the touch. There are two or three purple patches of skin on other parts of the left lower limb, which, Dr. Weber thinks, may be regarded as minute erythromelalgic islets.

There is no distinct cyanosis of the face and extremities, such as has been noted in most other cases of polycythæmia with splenomegaly, although the tongue, and sometimes the fingers also, are of a bright red colour with a bluish tinge, resembling the colour of raw butcher's meat. No disease can be detected in the heart or lungs. There is no dyspnœa. The cardiac apex-beat is in the fifth left intercostal space, internal to the nipple line, and the area of cardiac dulness is not increased. The radial pulse is about 88 in the minute and regular (though the rate is markedly affected by any mental excitement); it is of medium volume and generally rather increased tension. By abdominal palpation nothing abnormal can be detected except enlargement of the spleen, which is felt rather hard and extending two finger-breadths below the costal margin. Menstruation regular. Some tendency to chronic constipation. The urine is at present abundant, pale, of specific gravity about 1010, and free from sugar and albumen; but on a former occasion a trace of albumen was noted.

Examination of blood: Hæmoglobin, about 125 per cent. of the normal; red cells, about 9,000,000 in the c.mm.; white cells, about 8100. The differential count (Dr. G. L. Eastes, April 13) of white cells gives small lymphocytes 17·25 per cent., large lymphocytes 8·5 (total lymphocytes 25·75), polymorphonuclears 73·75, eosinophiles 0·5. During a count of 400 white cells one mast cell was found. No myelocytes or erythroblasts were detected.

On a subsequent occasion (April 19, late afternoon) Dr. J. H. Drysdale kindly examined the blood from the patient's finger and found that the red corpuscles numbered 8,660,000 per cubic millimetre, and the white cells 9000. This confirms the previous counts in regard to the polycythæmia. Dr. Drysdale also reported that the differential count of the white cells (polymorphonuclears 77·6, lymphocytes 18·5, large mononuclears 3·5, and eosinophiles 0·3 per cent.) did not differ much from that in ordinary persons.

There is slight deafness, possibly due to dry catarrh, and occasionally a subjective "roaring" sound is complained of. Knee-jerks obtained with some difficulty on both sides. There is slight wasting of the calf of the left leg (2 cm. difference in circumference, 14 cm. below knee-caps). A radiogram shows that the bones of the toes and distal part of the tarsus in the left foot give a decidedly fainter shadow to Röntgen's rays than in the right foot.

In many respects the present case resembles that recently brought before the Society by Drs. Weber and Watson, in which, however, there was no erythromelalgia (March 11, 1904). The association of splenomegalic polycythæmia with erythromelalgia has already been noted by W. Türk, of Vienna (*Wiener klinische Wochenschrift*, 1904, Nos. 6 and 7).

Treatment.—The acute erythromelalgia in the present case rather suddenly subsided whilst faradism was being tried, but nothing has seemed to influence the chronic condition. For various reasons the patient is now to be put on a diet consisting chiefly of milk.

Addendum.—The general condition appeared to remain uninfluenced by treatment, and the milk diet was not long continued owing to great objection on the part of the patient. On the morning of May 30, 1904, an examination of the blood showed hæmoglobin 165 per cent. of the normal; red corpuscles 10,600,000 in the cubic millimetre, white cells 7200. Small doses of arsenic (two to three drops of Fowler's solution three times daily) had been tried for the three weeks preceding this blood count, but were then discontinued. Dr. G. L. Eastes kindly examined blood-films taken on May 30, and confirmed the absence of myelocytes, of erythroblasts and of any poikilocytosis. The differential count of 300 white cells gave small lymphocytes 26·5 per cent., large lymphocytes 4·0, polymorphonuclears 68·8, eosinophiles 0·7.

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