from the surrounding medium as the substance of the nucleus is separated from the cytoplasm by a membrane—cell wall. Whilst this structure may well serve to retain within the cell the cell contents, including zymogens, ferments, and other colloidal bodies, it will readily permit the passage outwards and also inwards of those diffusible substances in solution, which we have just seen in virtue of their solution have undergone ionic dissociation. It is also obvious that the degree of concentration of the fluid with which the cells are bathed and, adopting the terminology of Croft Hill, of the ana- and kata- products of metabolism will very considerably affect the nature and extent of the intracellular changes—that is to say, of the ferment action—that is to say, of the cell activity. The amount of water taken up or lost by a cell will thus influence very materially the direction of its action determining a synthetic or an analytic result.

I just now said that Professor Loeb has demonstrated that muscle varied in its contractility according to the electrolyte with which it is surrounded; thus sodium salts favour contraction as potassium and calcium salts inhibit it, but although this is the action of calcium it is nevertheless found that its presence in very minute quantities along with the sodium salt considerably prolongs the contractility of the muscle; with this circumstance it may be remembered, as suggesting the direction in which these salts act, that though the "influence of calcium is of doubtful value in the production of muscle-clotting or rigor mortis, its presence is most important in blood-clotting and milk-curdling" (Halliburton), all which changes are the result of ferment action upon which it may be supposed the influence of the calcium ions is brought to bear. In these cases the salt solutions are dilute; a concentrated solution of sodium chloride would kill a muscle immersed in it.

As giving some support to this theory of ionic action, Mr. S. W. Cole, as the result of experimental work on the influence of electrolytes on the action of amylolytic ferments,[14] found "that the action is favoured by anions and depressed by cations." This conclusion was justified by finding "that the salts of the strong acids accelerate the action of ptyalin on starch; the accelerating influence being the greater, the greater is the strength (avidity) of the acid. With salts of weak acids there may be a retardation; the more pronounced the weaker the acid is, and especially prominent in salts of dibasic and tribasic acids." Dr. Mathews, also, finding that some salts stimulate as others depress nerve action, attributes the stimulant effects to the action of anions and the depressing effects to positive ions.[15] In confirmation of this it is known that the electrical stimulation of a nerve always proceeds from the negative pole (cathode) on making the current.

Much work has been recently done on the intimate nature of colloids, of which the proteids that form the bulk of protoplasm consist. Constituted of small granules held in solution they are found to be capable of bearing an electrical charge, positive or negative, to be, that is to say, electrolytes, and among these bodies the ferments are to be included. "The salts or electrolytes in general," says Professor Loeb,[16] "do not exist in living tissues as such exclusively but are partly in combination with proteids. The salt or electrolyte molecules do not enter into this combination as a whole but through their ions. The great importance of these ion-proteid compounds lies in the fact that by the substitution of one ion for another the physical properties of the proteids change (for instance, their power to absorb water and their state of matter)." "It is more than probable that one or both of these qualities may account for muscular contractility and protoplasmic motion. The agencies which affect these two variable qualities of the protoplasm are, first of all, certain enzymes. Almost equally powerful are ions in certain concentrations."

Thus, then, the vital activities of the living cells would seem to consist essentially in the formation of ferment bodies which alone or in combination effect those integrations and disintegrations which liberate chemical energy and that this by transformation produces muscular work, nerve force, and secretory function, the fundamental manifestations of life. That these enzymes do bring about these changes in such conditions of temperature and alkalinity or acidity as obtain in the body appears to be certain; and as an explanation of the activity of the bioplasm which elaborates these bodies there is postulated an ionic action on the part of the cell contents and their surrounding medium whereby charges of electricity of variable strength and character are brought into conflict and that from the play of ions the manifestations of vitality result. Such a conception of bioplastic activity leads more clearly to the realisation of the inseparable unity of function and nutrition, and that nutrition in its fullest sense is life itself.

[14] Journal of Physiology, November and December, 1903.
[15] Science, 1903, vol. xvii., p. 729.
[16] Studies in General Physiology, Collected Papers, 1905, Part II., pp. 544 and 622.

A CASE OF "SPLENOMEGALIC" OR "MYELOPATHIC" POLYCYTHÆMIA WITH TRUE PLETHORA AND ARTERIAL HYPERTONIA, WITHOUT CYANOSIS.[1]

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IN the absence of cyanosis the following case differs from the cases of chronic cyanosis with polycythæmia and splenomegaly recorded by Vaquez, Saundby and Russell, Rosengart, Osler, and others. I have had the advantage of being able to study a typical example of such cases[2] and believe that the present case is really of the same nature but at an earlier stage and occurring in a fairly robust subject whose circulatory system is acting efficiently. I would temporarily include all these cases, with or without cyanosis, under one heading—namely, "splenomegalic polycythæmia," although I think it possible that the spleen need not be obviously enlarged to clinical examination in all cases. In many respects cases of this group, like the present one—that is to say, cases without cyanosis—resemble the case of "hypertonia polycythæmica" (Geisböck) recently recorded by Hess[3] but apparently differ from it in the absence of albuminuria and in the presence of splenomegaly.

The present patient, a Jewish woman, aged 37 years, of medium height and weight, first came under my care in July, 1903, for acute erythromelalgia of the left foot.[4] This condition under rest in bed and other treatment became less acute and finally gradually disappeared. The existence of the polycythæmia was first detected when the blood was examined in March, 1904, but was probably present earlier. From April, 1904, to February, 1905, the patient was constantly under observation in the German Hospital and on April 22nd, 1904, was shown at a clinical meeting of the Clinical Society of London. Owing to the disappearance of the erythromelalgia she is no longer confined to her bed. In fact, the condition for which she originally came under treatment is practically cured, though her other symptoms, objective and subjective, persist, and it is with these that the present paper deals.

There is no distinct cyanosis of the face, though the cutaneous blood-vessels are somewhat overfilled and the tongue is generally of a bright red colour with a bluish tinge resembling the colour of raw butcher's meat. The toes, especially those of the left foot, sometimes appear rather livid, but this is possibly connected with the past erythromelalgia, which, it should be remembered, was not entirely confined to the left foot. No evidence of disease has been discovered in the heart or the lungs. There is no dyspnœa. By examination of the abdomen nothing abnormal can be detected excepting moderate enlargement of the spleen, which can be felt one or two fingers' breadth below the ribs. For diagnostic purposes, owing to a question of the possibility of splenic tuberculosis, Koch's old tuberculin was employed in December, 1904, but the injection of five milligrammes failed to produce a reaction. Menstruation is regular. The bowels are sometimes confined. The urine is usually

[1] A paper read before the Royal Medical and Chirurgical Society of London on May 9th, 1905.
[2] F. Parkes Weber and J. H. Watson: Chronic Polycythæmia with Enlarged Spleen, Transactions of the Clinical Society of London, 1904, vol. xxxvii., p. 115, and International Clinics, 1905, vol. iv., p. 47.
[3] Abstract by Pappenheim in the Folia Hæmatologica, 1905, vol. ii., p. 47. Cf. Geisböck: Verhandlungen der XXI. Kongresses für Innere Medicin, 1904, p. 97.
[4] I described this part of the case in the British Journal of Dermatology, February, 1904, p. 70.

TABLE I.—SHOWING BLOOD COUNTS IN RELATION TO TREATMENT, ETC.

Date.	Hæmoglobin per cent. of normal standard.	Red cells per cubic millimetre.	White cells per cubic millimetre.	Polymorphonuclears per cent.	Small lymphocytes per cent.	Large lymphocytes, large mononuclears, and "transitionals" per cent.	Coarsely granular eosinophiles per cent.	Mast cells per cent.	Erythroblasts (all normoblasts).	Average diameter of erythrocytes.	Diet and treatment.
1904.											
April 13th (*a*)	120	8,240,000	6000	73·75	17·25	8·5	0·5	Only one seen.	—	—	—
,, 17th	125	9,440,000	8100	—	—	—	—	—	—	—	—
,, 19th (*b*)	—	8,660,000	9000	77·6	18·5	3·5	0·3	—	—	—	At the end of April, 1904, a milk diet was ordered but was only continued for a few days owing to the patient's objection to it. She was then put on ordinary meat diet and from May 9th was given from two to three drops of liquor arsenicalis three times daily. The arsenic was discontinued on May 30th.
May 30th (*c*)	165	10,600,000	7200	68·8	26·5	4·0	0·7	—	—	Not greater than the normal.	—
June 12th	170	—	—	—	—	—	—	—	—	Great variety in size noted.	—
,, 20th (*d*)	148	10,960,000	8800	—	—	—	—	—	—	—	At the end of June, 1904, meat was discontinued, and the diet was made to consist of milk, milk puddings, bread, butter, potatoes, green vegetables. and stewed fruit, with every day two eggs and about twice weekly some fish. From July 8th, 1904, till February, 1905, she took the juice of one lemon daily.
July 8th	175	9,440,000	8400	—	—	—	—	—	—	—	—
August 3rd (*e*)	148	8,016,000	8000	—	—	—	—	—	—	—	—
,, 15th (*f*)	177	9,840,000	—	77·0	13·0	8·0	0·4	1·6	Present.	7·48 μ	—
,, 26th (*g*)	177	9,680,000	6000	—	—	—	—	—	—	—	—
Sept. 9th (*h*)	175	9,850,000	6000	—	—	—	—	—	—	—	—
,, 29th	185	9,800,000	—	—	—	—	—	—	—	—	In September the diet was changed so as to include fish or meat every day at the mid-day meal. From Sept. 15th to Oct. 8th Roentgen ray treatment was carried out; 21 sittings of from five to ten minutes' exposure of the splenic region. At several sittings the lower parts of the legs were likewise exposed for five minutes.
Oct. 14th	184	9,968,000	7320	—	—	—	—	—	—	—	—
Nov. 16th.	177	9,976,000	8320	—	—	—	—	—	—	—	From Oct. 31st to Dec. 5th, 1904, three grains of iodide of potassium were given three times daily.
,, 30th (*i*)	156	8,480,000	8200	81·0	12·6	5·6	0·6	0·2	Several.	7·74 μ	—
Dec. 9th (*j*)	—	—	—	73·0	15·0	8·4	3·0	0·6	,,	—	—
,, 16th (*k*)	158	—	—	72·6	14·0	7·0	1·0	0·4	,,	—	—
,, 23rd (*l*)	161	9,280,000	4800	—	—	—	—	—	—	—	Venesection, 100 cubic centimetres.
1905.											
Jan. 3rd	156	8,625,000	7500	75·4	18·6	5·4	0·6	Present.	Present.	—	—
,, 12th (*m*)	145	9,568,000	6000	66·0	25·4	6·6	2·0	,,	,,	—	During the last days of December to Jan. 12th the patient was taking 15 grains of bromide of potassium and seven and a half grains of aspirin thrice daily. From Jan 12th to Feb. 6th, 1905, she took ten grains of salicylate of sodium thrice daily.
1st	148	8,568,000	4000	75·0	11·0	11·6	2·0	0·4	,,	7·6 μ	—
Feb. 6th	164	8,680,000	4800	80·4	14·0	4·0	1·0	0·6	,,	—	—

Remarks.—(*a*) The differential count was of 400 white cells by Dr. Eastes. During the count one mast cell was found. There were no myelocytes or erythroblasts. Three or four of the white cells counted were "intermediate forms" and Dr. Eastes enumerated these with the type which they most resembled. (*b*) This blood count was made by Dr. Drysdale when he kindly came to see the patient. The large lymphocytes were counted with the small lymphocytes as "lymphocytes." I have therefore included them in the group of small lymphocytes; Dr. Drysdale is not responsible for this. (*c*) Dr. Eastes made the differential count and reported that no myelocytes or erythroblasts were seen and that there was no poikilocytosis. Films were likewise sent to Professor H. Vaquez, who mentioned in his paper with Dr. C. Laubry that they confirmed his opinion that in splenomegalic polycythæmia there was no hyperglobuly, that is is to say, increase in the average diameter of 100 red cells, though microcytes and macrocytes might be present. (*d*) Dr. Wright kindly took away specimens of the blood and urine for examination (see later). His count made the red blood corpuscles just over 11,000,000 in the cubic millimetre, a result not very different from that of the count at the hospital. (*e*) This count was taken after unusually copious menstruation. (*f*) The differential count was of 500 white cells by Dr. Boycott. He found the average diameter of 50 red cells to be 7·48 μ; the maximum diameter 8·57 μ; and the minimum diameter 5·95 μ. (*g*) In August it was noted that the patient could walk about without the left foot becoming hot or different in colour from the right foot. (*h*) The specimen of blood from which this count was made was obtained directly from a superficial vein in the right forearm by a Pravaz syringe. (*i*) The blood examination is by Dr. Boycott. During the differential count of 500 white cells he found three normoblasts, one with polychromatic cytoplasm and about 12 polychromatic red cells. The red cells varied from 4 μ to 10 μ in diameter and there were too many oval and irregular shapes. The hæmoglobin was estimated by Dr. Haldane (see also later). (*j*) The red cells, Dr. Boycott said, showed the same abnormal variation in size, shape, and staining capacity as at the last examination. He soon found several normoblasts and some polychromatic red cells. (*k*) The hæmoglobin estimation was by Dr. Haldane. (*l*) The blood examination was of blood obtained by venesection containing 1 per cent. of a 50 per cent. aqueous solution of citrate of potassium. (*m*) The differential counts in 1905 were all of 500 white cells by Dr. Boycott as were all the others from Nov. 30th. Dr. Haldane estimated the hæmoglobin on Jan. 21st. In the blood films of Feb. 6th Dr. Boycott thought the changes in the red cells were much less marked than before and could only discover one normoblast with great difficulty.

rather pale, acid, of low specific gravity (about 1010), somewhat increased in quantity, and free from albumin and sugar. The percentage of urea has not been regularly estimated. On one occasion it was 1·9 per cent., making the total daily excretion up to, or somewhat above, the average. The body weight on June 21st, 1904, was 10 stones 6 pounds. On August 23rd it was 10 stones 10 pounds; on Nov. 21st it was 11 stones. On Feb. 6th, 1905, it was 11 stones 2 pounds. Slight enlargement of the thyroid gland was temporarily noticed in October, 1904. There is considerable deafness in both ears, possibly connected with chronic dry catarrh. The patient's subjective symptoms consist in a disagreeable noise in her ears and occasionally headache and slight vertigo; also apparently feelings of prostration. The noise in her head is always present but varies in character from a whizzing or rushing to a roaring or rumbling sound and is rhythmical with the heart's action. I will now give an account of the examination of the blood and circulatory system whilst the patient has been under observation.

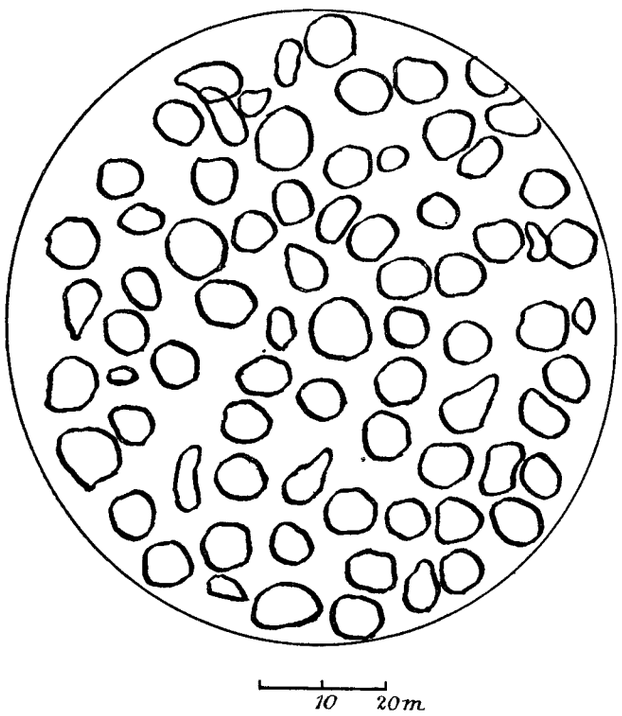
Circulatory system.—As already mentioned, nothing abnormal has been found by physical examination of the heart, the apex beat being in the fifth left intercostal space internal to the nipple line and the area of cardiac dulness not being increased. The pulse at the wrist is of medium volume and increased tension; it is regular, the rate being about from 80 to 90 in the minute, but affected by mental excitement. Pulse tracings made with a Dudgeon's sphygmograph in June, 1904, showed a pulse of high tension. On Dec. 20th, 1903, Hill and Barnard's pocket sphygmometer on the radial artery gave the mean blood pressure as about 140 millimetres of mercury (that is, the pressure at which the oscillations were greatest), but their larger instrument on the arm showed a pressure of about 165 millimetres of mercury. On Dec. 16th, 1904, Dr. J. S. Haldane kindly estimated the maximum brachial blood pressure by Martin's modification of the Riva-Rocci apparatus and found it to be 157 millimetres of mercury and on Jan. 21st, 1905, he found it 152 millimetres of mercury. In June, 1904, Dr. R. Gruber kindly made an ophthalmoscopic examination of the blood-vessels in the fundus oculi and reported that the veins were markedly congested and slightly tortuous but the macular region did not show any decided enlargement of capillaries such as he had noted in the case of chronic cyanosis and polycythæmia[5] already alluded to.

The blood.—The following table is intended to show the results of blood counts[6] and microscopic examination of the blood in relation to diet and treatment from March, 1904, to February, 1905. It must be remembered that owing to the improvement in the condition of the left lower extremity the patient was able to be up and to get about much more at the end of this period than at the beginning and this may have exercised an influence on the general condition.

In addition to the drugs mentioned in the table bromides, aspirin, and valerian were sometimes used. At the commencement of July, 1904, minute doses of calomel were tried for about a week but without any obvious effect on the general condition.

The red cells and hæmoglobin value.—The red cells varied abnormally in size, and according to Dr. A. E. Boycott in shape and staining capacity. These changes, together with the presence of a few nucleated red cells, might, as Dr. Boycott points out, be ascribed to unusual activity in the erythroblastic functions of the bone marrow. The nucleated red cells seen were all normoblasts and in the blood films from Nov. 30th, 1904, as many as three were noticed during a differential count of 500 white cells; in the blood from Dec. 16th 11 normoblasts were found on two slides in the course of a search of about three-quarters of an hour. Erythroblasts have likewise been observed by Türk and some others in cases of splenomegalic polycythæmia. In regard to the occasionalpresence of nucleated red cells in normal human blood, Dr. Boycott tells me that though probably present in all persons they are *extremely* rare. During the winter 1903–04 he searched about 500 blood films with this point in view and only found three or four altogether, though 500 leucocytes were counted in each specimen. The hæmoglobin values of the blood noted in April, 1904, were relatively low; probably the colour index of the corpuscles, and perhaps their size also, increased soon after this. The highest hæmoglobin values recorded were on Oct. 14th, 1904 (184 per cent.), and on Sept 29th (185 per cent.), but the hæmoglobinometers used on these occasions had not been specially standardised. The recent figures have varied from 145 to 164 per cent. The hæmocytometer readings have on the whole varied less that the hæmoglobinometer readings. The largest number of red cells recorded was 10,960,000 on June 20th, 1904, and the lowest was 8,016,000 on August 3rd; at present (Feb. 6th, 1905) there are about 8,500,000 in the cubic millimetre and the average colour index of the cells is nearly up to the normal.

FIG. 1.



Red blood corpuscles showing variations in size and shape in a film taken on August 15th, 1904. Drawn to scale by Dr. Boycott.

Vaquez[7] is probably right in saying that in splenomegalic polycythæmia, even when combined with marked cyanosis, there is no "hyperglobuly"—that is, that the average size of the red cells, judged by their average diameter, does not exceed normal limits. In my last case[8] it did not and in the present case it does not, for Dr. Boycott estimated the average diameter at 7·7 μ on Nov. 30th, 1904, and at 7·6 μ on Jan. 21st, 1905.[9] In an old preparation from August 15th, 1904, he made it only about 7·5 μ. In this connexion it is interesting that Dr. A. E. Wright,[10] who kindly examined the patient's blood on June 20th, 1904, counted the red cells as just over 11,000,000 in the cubic millimetre, and in the sedimentation tube obtained 9·25 volumes instead of the ordinary five volumes of corpuscles in ten volumes of blood. It may here be recalled that J. A. Capps, in his "Study of Volume Index,"[11] concluded that the volume of the individual erythrocyte is best obtained by using the centrifuge in conjunction with the hæmocytometer.

The white cells.—In regard to the white cells the first thing to be noticed is the relative leucopenia, which has lately been very pronounced, the count having been on three occasions as low as from 4000 to 5000 in the cubic millimetre of blood. Relative leucopenia has, however, not been a feature in all cases of splenomegalic polycythæmia. The second point is the high percentage of polymorphonuclears, from

[5] Weber and Watson, loc. cit.

[6] The blood counts were made by a Thoma-Zeiss's hæmocytometer and the hæmoglobin value was obtained either by a Gowers's hæmoglobinometer or by Haldane's modification. In the later estimations (Nov. 30th and later) either a correct Haldane's instrument was used or an old Gowers's instrument freshly standardised by the kindness of Dr. Haldane and Dr. A. E. Boycott. The instruments used in the earlier estimations were not freshly standardised. I had the pipette of a Gowers's hæmoglobinometer graduated so that only half the usual amount of blood might be sucked up. In this way the diluted blood does not rise above the scale.

[7] Vaquez: Du Volume des Globules Rouges dans les Polyglobulies avec Cyanose, Société de Biologie, Paris, July 16th, 1904.

[8] See Weber and Watson, loc. cit. The average diameter was 7·11 μ.

[9] Dr. Boycott used ordinary stained blood films for this purpose, measuring from 50 to 100 cells on each occasion.

[10] On the Volumetric Estimation of the Corpuscular Elements, THE LANCET, Jan. 23rd, 1904, p. 216.

[11] Journal of Medical Research, Boston, December, 1903, vol. x., p. 367.

66 to 81. This, Dr. Boycott thinks, forms additional evidence of unusual activity in the bone marrow. In my previous case of splenomegalic polycythæmia[12] the polymorphonuclears constituted 82·4 per cent. of the total white cells and Vaquez[13] found the proportion to be from 79 to 82 per cent. No myelocytes were found in the blood from either of my cases.

Total volume of the blood.—Dr. Haldane kindly came three times to estimate the total quantity of the patient's blood by his carbon-monoxide method.[14] After the last visit he wrote that not only was there no doubt at all as to the enormous increase in the red corpuscles and hæmoglobin but that he also felt convinced that the last blood volume determination (Jan. 21st, 1905) left no loop-hole of error as to there being also a large increase in the blood volume, though not so large as in many cases of chlorosis, according to Professor J. Lorrain Smith's estimations. The following are Dr. Haldane's figures of his first determination (Nov. 30th, 1904) and of his third determination (Jan. 21st,1905). He thinks that there was certainly an error in his second determination (Dec. 9th, 1904) which has therefore been omitted.

TABLE II.—*Showing Figures connected with the Estimation of the Total Volume of the Blood by the Carbon Monoxide Method.*

Date.	Volume of CO in cubic centimetres at 0°C. and 760 millimetres barometric pressure.	Saturation of hæmoglobin per cent.	Total oxygen capacity of blood in cubic centimetres.	Percentage of hæmoglobin.*	Total volume of blood in cubic centimetres.†	Red corpuscles in cubic millimetre of blood.	White corpuscles in cubic millimetre of blood.	Body weight in kilogrammes (clothes allowed for).	Cubic centimetres of blood per 100 grammes body weight.	Oxygen capacity per 100 grammes body weight in cubic centimetres.
1904.										
Nov. 30th.	74·0	4·6	1610	156	5600	8,480,000	8200	68	8·2	2·4
1905.										
Jan. 21st.	127·0	7·0	1810	148	6000	8,568,000	4000	68	9·7	2·7

* The normal percentage of hæmoglobin is reckoned as 100. It may be added that 100 cubic centimetres of blood with this normal percentage of hæmoglobin can take up 18·5 cubic centimetres of oxygen.

† The normal individual is estimated to possess 4·6 cubic centimetres of blood per 100 grammes body weight.

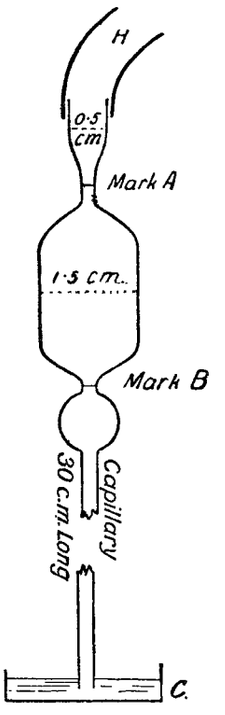
The residue of carbon monoxide was analysed after each experiment to ascertain its degree of purity and the air left in the bladder was also analysed to make certain that the carbon monoxide had been actually absorbed.

Amount of iron in the blood.—Some blood (45¾ grammes) after serving for the viscosity and cryoscopy examinations was used by Mr. J. H. Ryffel, B.Sc., to obtain a quantitative estimation of the iron. He dried the blood in a platinum dish in the water oven, then ignited in the dish till all carbon was burnt away, dissolved the ash in strong hydrochloric acid, diluted, filtered, evaporated in a porcelain dish with a few drops of strong nitric acid, redissolved in dilute hydrochloric acid, precipitated with ammonia, filtered, washed, dissolved in dilute sulphuric acid, reduced with pure zinc, filtered through asbestos, and titrated with $\frac{N}{10}$ permanganate solution. Mr. Ryffel found that the percentage of iron, calculated for the undiluted blood, was 0·0673 gramme per cent. Dr. Boycott points out that supposing hæmoglobin to contain 0·33 gramme per cent. of iron Mr. Ryffel's result would correspond to 23·9 grammes of hæmoglobin per cent. in the blood; the 100 per cent. of Haldane's hæmoglobinometer standard corresponds to an oxygen capacity of 18·5 per cent., which is believed to be equivalent to 13·7 grammes of hæmoglobin per cent. in the blood; Mr. Ryffel's result would therefore correspond to 174 per cent. of hæmoglobin on Haldane's scale. The hæmoglobin actually found in the venesection blood was 161 per cent. Allowing, therefore, for a little iron in the white blood corpuscles (normal blood plasma is said to be free from iron) and for some evaporation (concentration of the blood) during the viscosity estimation, Mr. Ryffel's estimation of the total iron in the blood corresponds with the percentage of hæmoglobin found.

Specific gravity of the blood.—On June 27th, 1904, the specific gravity of a sample of the patient's blood obtained by pricking the finger was found to be 1·078 by the help of Hammerschlag's method. By the more accurate (pyknometer) weighing method the specific gravity of the blood obtained at the venesection on Dec. 23rd, 1904 (after being mixed with 1 per cent. of a 50 per cent. aqueous solution of potassium citrate) was found to be 1·072.

Viscosity of the blood.—I made use of the citrated blood obtained at the venesection on Dec. 23rd, 1904, to examine its viscosity by means of a viscosity tube exactly similar to the one suggested to me by Professor Arthur Schuster and made for me by Messrs. Baird and Tatlock, which I had employed with Mr. J. H. Watson in 1904[15] to ascertain the influence of the proportion of corpuscles on the viscosity of blood (in blood from a horse citrated to hinder coagulation). I found that the citrated blood from the patient took 203 seconds to run through the bulb of the tube, from one mark to the other, water taking only 19 seconds.[16] The specific gravity of the citrated blood was 1·072. Therefore, according to the formula given me by Professor Schuster, if n_1 = the coefficient of viscosity of the citrated blood and n = the coefficient of viscosity of water at the temperature at which the experiment was made, $n_1 = \frac{n \times 203 \times 1{\cdot}072}{19 \times 1{\cdot}000}$. Therefore the coefficient of viscosity of the citrated blood was 11·45 times the co-efficient of viscosity of the water used. Unfortunately, the temperature of the water used was not taken and it may have been below the temperature of the room, which was about 18·4° C. Evidently, however,

FIG. 2.



The liquid is sucked up from an open vessel, C, by means of an indiarubber 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. If the time taken in two different liquids be t_1 and t_2 respectively, and p_1 and p_2 be the respective densities of the two liquids, and 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.

[12] Weber and Watson: Loc. cit.

[13] Vaquez and Laubry: Cyanose avec Splénomégalie et Polyglobulie, Tribune Médicale, Paris, August 13th, 1904, p. 517.

[14] Vide J. Haldane and J. Lorrain Smith: The Mass and Oxygen Capacity of the Blood in Man, Journal of Physiology, August 29th, 1900, vol. xxv., p. 331.

[15] Vide Weber and Watson: Transactions of the Clinical Society of London, 1904, vol. xxxvii. (the apparatus used is described and figured on p. 131).

[16] The tube previously used for the experiments with horse's blood was not used on this occasion because water took about 44 seconds to run through the bulb and the estimation of the viscosity of the patient's blood would have taken an unnecessarily long time.

the viscosity of the blood was excessive, higher than that of blood in all ordinary diseases and conditions.

Cryoscopy of the blood.—Some blood obtained at the venesection on Dec. 23rd, 1904 (mixed with 1 per cent. of a 50 per cent. aqueous solution of potassium citrate), was employed by Dr. W. d'Este Emery, clinical pathologist at King's College Hospital, to determine the freezing point, which he very kindly did on the day on which the blood was obtained. After the slight correction necessary for the presence of potassium citrate the freezing point was found to be minus 0·53° C., and therefore not very different from that of normal blood, which is about minus 0·56° C. The urine passed by the patient immediately after the venesection was of specific gravity 1008, faintly acid, and free from albumin and sugar. Dr. Emery found its freezing point was minus 0·79° C. Dr. Emery added that the blood plasma could not be collected in amount sufficient for the estimation of the freezing point, as after thorough centrifugalisation of a specimen of the citrated blood the plasma layer was only about two millimetres thick or, roughly speaking, only about 3 per cent. of the blood column.

The salts in the blood and urine.—On June 20th, 1904, Dr. Wright[17] estimated the salts in the blood as equivalent to 0·58 per cent. of sodium chloride (in lieu of the normal about 0·78 per cent.), the salts of the urine[18] coming out as equivalent to 0·46 per cent. of sodium chloride. This, Dr. Wright says, gives an excretory quotient of about 0·8 instead of the normal of over 2·0. However, on June 26th, 1904, he estimated the salts in the blood serum as equivalent to 1·14 per cent. of sodium chloride, whilst the salts in the fluid from a blister were equivalent to 0·95 per cent. of sodium chloride.

The alkalinity of the blood.—Dr. Wright estimated this on June 26th, 1904, as equivalent to that of a normal alkaline solution diluted 35 times. He expresses it as $\frac{N}{35}$.

The amount of albuminous substance in the blood plasma.—Dr. Wright found the amount in the citrated blood obtained on Dec. 23rd, 1904 (at the venesection), to be normal. His method of measuring the albuminous substances is by the resistance of the clot obtained by heating a graduated series of dilutions of the plasma.[19]

The coagulation of the blood.—Dr. Wright thought its occurrence was very much delayed on June 20th, 1904. Afterwards it appeared to occur fairly readily, but the exact coagulation time was not estimated.

The resistance of the red cells to hæmolytic agents.—Dr. Wright examined the citrated blood taken Dec. 23rd, 1904, by a method of his own and found the resistant power of the red cells to be about normal. One volume of centrifugalised sediment of red cells (the red cells were by repeated centrifugalisation washed fairly clean of blood-plasma) was suspended in sufficient $\frac{N}{10}$ salt solution to bring the total volume of the suspension up to three volumes. Complete hæmolysis was then obtained by adding one volume of the suspension in a capillary tube to one volume of a $\frac{N}{30}$ salt solution.

EFFECT OF TREATMENT AND PROGRESS OF THE CASE.

As already stated, it is exceedingly difficult to estimate how much the patient's condition has really altered apart from the improvement in the erythromelalgic extremity. She can now walk about quite well and has gained in weight, the erythromelalgia has disappeared, but the polycythæmia, high arterial tension, and the other phenomena in the blood and circulatory system persist, as do likewise the subjective symptoms (headache, &c.), although they vary in degree from time to time. Arsenic, which was employed by W. Türk[20] in his cases, was soon discontinued in the present case on account of a considerable apparent increase in the number of red corpuscles which followed its use. On the whole the patient has seemed to be better when on a diet containing relatively little meat and when taking lemon juice daily. It is possible that small doses of iodide of potassium or salicylates have a favourable influence. I have little doubt that absolute rest in bed, which was at one time required owing to the erythromelalgia, has an injurious influence on the general condition and some of the slight apparent improvement in the general condition may be due to the patient having been able to take a little exercise (favouring metabolic processes). Opium and its derivatives have not been given a trial. In regard to drugs, such as phenacetin and antifebrin (acetanilide), it must not be forgotten that the chronic use of antifebrin seems to give rise to cyanosis and blood changes.[21]

The venesection in the present case seemed to make no difference in the subjective or objective condition and it was not repeated, but perhaps the amount of blood (100 cubic centimetres) withdrawn was too little to produce any decided change. It may be noted also that the diminution in the number of red blood corpuscles observed on August 3rd, 1904, followed unusually copious menstruation.

The employment of Roentgen rays, which has lately been found to have such a decided effect in many cases of leukæmia, seems to have made no change in the number of red blood corpuscles in the present case. This is not to be wondered at since the action of these rays on the spleen and hæmopoietic tissues in leukæmia seems to be chiefly on the lymphocytes ("lymphocytolysis") and lymphadenoid tissues and on the leucocytes generally ("leucolysis").[22] It is, however, to be noted that after a good many Roentgen-ray sittings the patient complained more of headache or feeling of congestion in the head and this decided us to discontinue the treatment. The number of white cells in the cubic millimetre has been particularly low at recent counts (see Table I.) and the spleen has not been so easy to feel. It is possible, therefore, that the Roentgen rays, though they had no influence on the number of red blood cells, may have had a slight tardy effect on the spleen and on the formation of white cells analogous to that recorded in cases of leukæmia. The Roentgen-ray treatment was carried out by Dr. Mülberger, senior house surgeon at the German Hospital, who employed apparatus of Siemens and Halske of London, with direct street main supply; spark gap 25 centimetres; mercury dip break; 220 volts; 10 amperes; frequent breaks; hard tube (C. H. Müller, of Hamburg, No. 13, with vacuum-regulating apparatus); distance of the patient's skin from anticathode 50 centimetres; diaphragm compressor according to Dr. Faulhaber of Würzburg. The splenic region was subjected to the treatment for five minutes at every sitting and for one minute in addition every subsequent sitting till ten minutes were reached, after which the time of exposure was not changed. The treatment was carried out regularly, one sitting every day (Sundays excepted), from Sept. 15th to Oct. 8th, 1904, 21 sittings altogether. At nearly all of these sittings the lower parts of the legs were likewise exposed to the rays for five minutes.

In regard to future treatment it will be important to observe how the patient progresses now that she has left the hospital; in fact, the question is whether any special treatment is at present advisable or not. In the absence of all evidence that the disease is primary in the spleen I do not think that the operation of splenectomy can be recommended

REMARKS AND CONCLUSIONS.

As stated at the commencement of this paper I regard the present case, in spite of the absence of cyanosis, as similar in nature to my previous case[23] of splenomegalic polycythæmia. The excess of red corpuscles, true plethora ("polyhæmia") and arterial hypertonia were present in both cases. In the previous case the polycythæmia with the resulting increased viscosity of blood and increased strain on the circulatory mechanism was doubtless of older standing, the patient's vital powers were probably on the decline, and the cyanosis and relatively scanty urine may have been a result of a gradually developing inadequacy of the circulatory mechanism to compensate for the great viscosity of the blood (in spite of the presence of high arterial blood pressure).

The conclusions arrived at in my paper with Dr.

[17] Vide Wright and Kilner on a New Method of Testing the Blood and the Urine, THE LANCET, April 2nd, 1904, p. 921.

[18] This was the urine passed directly after the examination of the blood, the bladder having been emptied before the examination. It was of specific gravity 1010, clear, rather pale, acid, and free from albumin.

[19] A. E. Wright: THE LANCET, Jan. 23rd, 1904, p. 218.

[20] Wiener Klinische Wochenschrift, 1904, Nos. 6 and 7.

[21] Stengel and White: A Report of a Case of Chronic Acetanilide Poisoning, with Marked Alterations in the Blood, University of Pennsylvania Medical Bulletin, Philadelphia. February 1903, p. 462.

[22] Cf. especially A. Wolff: Theoretisches über die Behandlung der Leukämien und Anämien mit lytischen Methoden durch Röntgenstrahlen und Leukolytische Sera, Wiener klin.-ther. Wochenschrift, 1904, No. 49

[23] Weber and Watson, loc. cit.

Watson as to a pathological activity in the production of erythrocytes in the bone marrow being the cause of the blood and circulatory phenomena have, I think, been amply confirmed by the present case. Our theoretical observations on a possible alteration in the osmotic tension of the blood may not have been required to explain the phenomena observed and, indeed, I shall not discuss that question here, as I have no fresh evidence to offer that there is any special change in regard to osmotic tension to be found in the symptom-complex under consideration.

In my previous case the existence of most extensive bone-marrow changes was proved by examination after death. A great portion of the normal bone marrow of the shafts of the long bones was found to have been replaced by red bone marrow, relatively free from fat, in which very active formation of red corpuscles was in progress as evidenced by the large quantity of erythroblasts. The changes were, however, not exclusively of an erythroblastic kind and it may be doubted whether the erythrocyte-producing functions of the bone marrow can ever be greatly increased without the myelocytes being to some extent involved in the unusual activity. Dr. Boycott has pointed out that in the present case an abnormal activity of the bone marrow may not only account for the excess of red cells in the blood, for the great variations in their size (and for the variations noted in lesser degree in their shape and staining capacity), and for the presence of nucleated red cells, but likewise for the high percentage of polymorphonuclear leucocytes. These changes have been found in other cases of splenomegalic polycythæmia. There is no evidence pointing to diminished destruction or lessened wearing out of red blood cells as a factor in the production of the anomalous blood condition. If the polycythæmia were due merely to concentration of the blood it would doubtless be only temporary and the blood would rapidly be diluted by fluid absorbed from the alimentary canal either directly into the blood capillaries or else into the lacteals to be thrown into the blood stream by way of the thoracic duct. Moreover, the fact that the total volume of blood in the body is abnormally great precludes the possibility that mere concentration of blood can be the cause of the blood changes. The clinical investigations of these blood changes, as already pointed out, as well as post-mortem examination, show that in cases of splenomegalic polycythæmia there is increased production of red corpuscles and I think the evidence is now really conclusive that the symptom-complex is always accompanied by, and at all events mainly due to, a pathological activity in the bone-marrow. Whether the latter condition can or cannot be regarded as the primary factor is a question to which I shall refer later. The objection to calling the symptom-complex "primary myelopathic polycythæmia" is that we are not sure that the disturbance of the bone marrow is necessarily the primary pathogenic factor; whilst the term "myelogenic polycythæmia" is insufficient, for every polycythæmia, excepting temporary states due to mere concentration of the blood, is "myelogenic" in the sense that the excess of red blood corpuscles is due to unusual activity of the bone marrow. On the other hand, the term "splenomegalic polycythæmia" only signifies that the spleen is usually enlarged, not that it must necessarily be found enlarged in every case.

I now believe the *order of development of the main symptoms* and their *causal connexion* to be as follows:—1. Increased erythroblastic activity involving a great part, but not necessarily the whole, of the bone marrow.[24] 2. Increased viscosity of the blood resulting from the polycythæmia. 3. Dilatation of small blood-vessels, partly to lessen resistance to the abnormally viscous blood, partly to make more room for dilution of the blood. 4. The "plethora vera" or "polyhæmia" is probably to be regarded as an attempt to compensate for the increased viscosity of the blood and for the excessive percentage of the total blood volume occupied by the cells. In fact, it is necessary, firstly, that there should be sufficient blood plasma to nourish the tissues and make metabolism possible; and, secondly, that the viscosity may not become so great as to render sufficient circulation impossible. 5. The arterial hypertonia is to be regarded as a result of the greater strain thrown on the circulatory mechanism. 6. Cyanosis, when this occurs, is probably due to inadequacy of the series of compensatory changes which, according to my view, precedes it.

In my opinion the evidence afforded by this and other cases strongly supports the foregoing conclusions, but the question now arises, *What is the nature of the pathological activity in the erythroblastic function of the bone marrow?* At least two theoretical explanations suggest themselves. In the first place that the bone-marrow activity is a primary one, allied to a tumour formation, or the result of an "idiosyncrasy" of the patient. One can suppose, for instance, that some persons have a bone marrow which reacts to ordinary erythroblastic stimuli to an excessive degree—viz., by throwing almost double the normal quantity of red cells into the blood stream. If, however, as H. Ribbert[25] believes there is a form of "myeloma"—that is to say, of growth originating in the elements of the bone marrow—which should be termed "erythroblastoma," because the tumour cells are related to erythroblasts, it seems possible that cases of splenomegalic polycythæmia, such as our two cases, may bear a relation to cases of erythroblastoma similar to that which lymphocytic leukæmia bears to lymphocytic myeloma.[26] The other explanation is that some toxin of a hæmolytic nature manufactured in the enlarged spleen or alimentary canal is absorbed into the circulating blood in minute quantities not sufficient to cause much hæmolysis but in amounts just sufficient to excite reaction in the hæmopoietic (erythroblastic) tissues. Metchnikoff quotes Belonovsky[27] of St. Petersburg as having increased both the number of corpuscles and the amount of hæmoglobin in the blood of anæmic persons by the injection of minute doses of hæmolytic serum.

I have just mentioned these possible alternatives in regard to the nature of the bone-marrow activity in splenomegalic polycythæmia, but they are merely theoretical suggestions and I do not think it will be profitable to discuss them further without additional evidence.

The cause of the splenic enlargement.—If one inclines to the view that the bone-marrow condition in splenomegalic polycythæmia is the result of reaction to toxins circulating in the blood it is natural to suggest that the enlargement of the spleen is due to the same toxins, whether they enter the circulation from the intestines or elsewhere, or else that there is a primary disease of the spleen, such as tuberculosis (as there actually was in the case of Rendu and Widal[28] and some other cases), which gives rise to a condition of toxæmia to which the bone marrow reacts (excessive reaction being explained by idiosyncrasy) by an erythroblastic reaction resulting in polycythæmia. In favour of such a view there is the fact that in Saundby and Russell's case of splenomegalic polycythæmia with cyanosis Dr. J. W. Russell saw the patient with an enlarged spleen several years before cyanosis developed. To this I would answer that the polycythæmia was probably likewise present for years before the cyanosis developed and that cyanosis, if the views I have brought forward are correct, is not an essential part of the symptom-complex.

In my present case the enlargement of the spleen is not excessive and does not appear to be progressive and there is no fever or reaction to tuberculin to suggest the presence of tuberculosis. Splenic tuberculosis is certainly not necessarily present in cases of splenomegalic polycythæmia and primary tuberculosis of the spleen is not necessarily accompanied by polycythæmia.[30]

Possibly in the cases in which the splenic enlargement is due merely to increase of the pulp and engorgement with blood, as it seems to have been in my previous case, it may be explained as being due to the plethora vera (polyhæmia) and high blood pressure or as resulting from excessive functional activity in attempting to compensate for the excessive production of red corpuscles by increased destruction. Of these two last alternatives the former seems to me

[24] In post-mortem investigations on these cases it would obviously, therefore, be a great mistake to be content with the examination of one portion of bone marrow. Part of the shaft of one long bone might be filled with bone marrow of the ordinary yellow fatty variety and yet the total active red-cell-forming bone marrow in the body might be more than three times the normal amount.

[25] H. Ribbert: Centralblatt für Allgemeine Pathologie, Jena, 1904, vol. xv., No. 9.

[26] Cf. F. Parkes Weber: A Case of Acute Leukæmia, with a Scheme of Classification of Leukæmias and Pseudo-leukæmias, Transactions of the Pathological Society of London, 1903, vol. liv., p. 286.

[27] Sur l'Influence de l'Injection de Diverses Doses de Sérum Hémolytique sur le Nombre des Eléments du Sang, St. Petersburg, 1902.

[28] Bulletin de la Société Médicale des Hôpitaux de Paris, 1899, p. 528.

[29] An Unexplained Condition of Chronic Cyanosis, THE LANCET, Feb. 22nd, 1902, p. 515.

[30] Cf. Y. Bayer, Ueber die Primäre Tuberkulose der Milz, Mitteilungen aus den Grenzgebieten der Medicin u Chirurgie, 1904 vol. xiii., p. 523.

the most probable, as there is as yet no evidence of greatly increased destruction of red cells in these cases either occurring in the spleen or elsewhere.

Relation of erythromelalgia to polycythæmia.—There is no certain causal relationship and in the present case the association of the two conditions may have been a chance one. Yet it must be remembered that the association of splenomegalic polycythæmia with erythromelalgia has already been noted by W. Türk[31] of Vienna. I have elsewhere[32] given my reasons for believing that in the so-called "idiopathic or neuropathic erythromelalgia," as well as in what might be termed "symptomatic erythromelalgia" (that is, severe pain and redness in an extremity affected with decided arterial obstruction), there is obstruction to the supply of arterial blood, at all events during the chronic stages. In the present case the muscular atrophy and absorption of bone salts in the affected extremity[33] at one time pointed to local deficiency of arterial blood-supply. It is possible that when for any reason the supply of blood to the bone marrow of a long bone is greatly diminished the bone marrow may make an attempt to manufacture more blood; in fact, may undergo a hæmopoietic (erythroblastic and leucoblastic) reaction. Through the kindness of my colleague, Dr. E. Michels, in 1904 I had the opportunity of examining the tibia removed by amputation from an extremity affected by chronic arterial obstruction. There was some red metaplasia of the bone marrow at the ends of the shaft. In this case, however, the bone-marrow reaction may have been connected with the septic pyrexia preceding the amputation. Dr. J. Galloway also kindly showed me a patient with pain and redness in one foot undoubtedly due to arterial obstruction and informs me that in that patient the blood has been repeatedly examined and the number of red cells has always been found considerably above the normal. Such an increase in the number of red blood corpuscles was, however, not present in another somewhat analogous case, and further information is needed to find out whether chronic ischæmia of an extremity, which can notoriously give rise to local muscular and osseous atrophy, can likewise produce changes in the bone marrow of the affected part besides those due to absorption of fat cells.

I have to thank all those who have so kindly assisted me in the examination of this case, without whose assistance I could not have arrived at my few conclusions—in the first place, Dr. Haldane, Dr. Boycott, and Dr. Wright, and then Dr. J. H. Drysdale, Dr. Emery, Mr. Ryffel, and Dr. G. L. Eastes, and also (not least) the house physicians at the German Hospital, Dr. R. Blendinger and Dr. Schuh.

ADDENDUM.—In cases of splenomegalic polycythæmia the onset of chronic cyanosis probably still further increases both the viscosity and the total volume of the blood. The effect of carbonic acid gas in increasing the viscosity of the blood has been clearly demonstrated by J. Bence[34] who states also that, according to Limbeck, an increase in the total volume of the blood accompanies the increase in the viscosity and adds that, according to Hamburger, this volumetric increase depends on an alteration in the osmotic relation between the red corpuscles and the blood plasma. Since writing the present paper I have come across an interesting account by W. Weintraud of three cases of splenomegalic polycythæmia.[35] The second of Weintraud's patients suffered also from a condition said to resemble erythromelalgia. In the same case, on one occasion, a remarkable improvement in the subjective symptoms followed a sharp attack of hæmatemesis.

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[31] Wiener Klinische Wochenschrift, 1904, Nos. 6 and 7.
[32] British Journal of Dermatology, February, 1904, p. 70.
[33] This was shown by radiograms of the two feet. Vide Transactions of the Clinical Society of London, 1904, vol. xxxvii., p. 250.
[34] Deutsche Medicinische Wochenschrift, April 13th, 1905, p. 590.
[35] Zeitschrift für Klinische Medicin, 1904, vol. lv., p. 91.
[36] This does not include all the articles referred to in the footnotes.

SYMPTOMATOLOGIE ET DIAGNOSTIC DE L'ANGINE À SPIRILLES ET BACILLES FUSIFORMES (ANGINE DE VINCENT).

PAR LE PROFESSEUR H. VINCENT.

I.

LA maladie que j'ai décrite sous le nom "d'angine à spirilles et bacilles fusiformes" présente une fréquence attestée par les nombreuses publications parues sur ce sujet. Elle peut s'observer à tous les âges, mais elle est surtout fréquente chez l'enfant vers l'âge de 8 à 10 ans et chez l'adulte de 18 à 30 ans. Au delà de 35 ans, elle devient certainement plus rare. D'après mes statistiques, cette angine s'observe dans la proportion de 2·26 pour 100 cas d'angines de toute autre nature (diphtérique, streptococcique, staphylococcique, colibacillaire, etc.), chez les adultes.

Cette maladie existe dans tous les pays, sous tous les climats et chez toutes les races, y compris la race nègre. Elle n'épargne même pas ceux qui prennent soin de l'hygiène de leur bouche. Cependant, elle est plus fréquente chez les sujets malpropres, chez ceux qui abusent du tabac ou de l'alcool, chez ceux qui ont des dents cariées. Cette angine a aussi des relations avec l'évolution dentaire. Tantôt seule, tantôt associée à la stomatite ulcéro-membraneuse (qui est due, le plus souvent, ainsi que je l'ai démontré, à l'infection par les mêmes microbes) l'angine se manifeste assez souvent au moment de la deuxième dentition et à l'époque de l'éruption des dents de sagesse. L'influence particulièrement favorisante du terrain sur l'éclosion de cette infection locale, est démontrée par sa fréquence chez les sujets anémiés par la misère physiologique, affaiblis par le surmenage; chez les syphilitiques et les tuberculeux; chez ceux qui vivent dans des logements malsains, mal aérés. Cette angine a une certaine prédilection pour les étudiants en médecine qui font la dissection, pour les garçons d'amphithéâtre d'anatomie,