THE PATHOLOGIC PHYSIOLOGY OF PELLAGRA

V. THE CIRCULATING BLOOD VOLUME

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(Received for publication October 27, 1930)

Determination of circulating blood volume was undertaken as a part of a study of the disturbed physiology in pellagra, chiefly for the purpose of finding out whether shrinkage of plasma volume existed in patients who were suffering from a disease frequently characterized by severe diarrhea. Such a shrinkage would be of great importance of itself, and would obviously have a bearing upon the interpretation of the composition of the plasma determined at the same time. The existence of anemia can hardly be established nor its severity estimated so long as we are in ignorance of the plasma volume. It was also considered possible that the magnitude of the circulating blood volume might be correlated with certain of the features of the skin lesions, such as the degree of exudation of serum.

I have used the dye method of Keith, Rowntree and Geraghty (1) modified as follows: A 3 per cent aqueous solution of brilliant vital red (National Aniline Company) was made up the afternoon before use, and sterilized at 100°C. for 8 minutes. With a sterile calibrated pipette the quantity of this solution for each patient was placed in a sterile 50 cc. flask. The volume used for each patient was approximately 1 cc. for each 15 kilos of body weight. At the bedside, the dye was drawn from the flask through a sterile needle, which was then discarded, into a sterile Luer syringe which had just been rinsed with sterile distilled water. The dye left in the flask was taken up in a small quantity of sterile distilled water. After taking blood for chemical studies and to provide plasma for preparation of dye standard, the dye was injected through the same needle and the remaining dye washed out of the syringe with the patient's circulating blood by emptying and filling the syringe twice. After removal of the needle

the arm was elevated and no pressure used over the site of the venepuncture. Six minutes after first emptying the syringe of dye, blood was withdrawn from the other arm by venepuncture made a few seconds before. All blood used in the estimation of plasma volume was collected in an oiled syringe and run under oil with 10 mgm. of dry powdered potassium oxalate for each 5 cc. of blood. The blood was run under the oil from the syringe through a dry glass tube and rubber connection. Blood was run gently but quickly back and forth from centrifuge tube to syringe in order to insure rapid and complete mixing of oxalate with blood. With these precautions hemolysis was a rare occurrence. Blood was collected only after any stasis incident to venepuncture had disappeared. For determination of cell volume the hematocrit tube of Wintrobe (3) was used. The blood which contained dye was thoroughly mixed by drawing it in and out of a wide mouth 1 cc. pipette, and then the hematocrit was filled by means of a large calibre capillary pipette. It was centrifuged at 3000 revolutions for 30 minutes. The upper levels for both erythrocytes and leukocytes were read. The use of this hematocrit makes it possible to take the approximate white cell volume into account in calculations. Five per cent was added to hematocrit reading to allow for cell shrinkage. Two cubic centimeter quantities of plasma were used in preparing the standard and unknown dye solutions for the colorimeter. The final volume for each was 6 cc. Readings were made with a Dubosq colorimeter equipped with 5 cc. cups.

Since certain clinical manifestations of pellagra suggest increased capillary permeability, it was considered of importance to determine whether the dye might disappear from the blood stream with abnormal rapidity. Fifteen observations were made on patients during the various stages of pellagra, taking an additional dye-containing specimen of blood after intervals of from 4 to 24 minutes. The dye content of these second specimens showed that the maximum rate of disappearance was 4 per cent per 10 minute period and the average rate was one half as great.

How best to express the values for blood volume in this report has not been easy to decide. Most of the patients were greatly underweight. For some of them blood volume per kilo was normal or high, while blood volume per square meter of body surface was below the

recognized standards. It seems clear that neither method of expressing blood volume is satisfactory for such a group, unless corrections are made for abnormal body size. I have used the formula of Rowntree and Brown (2). It provides corrections for the factors of underweight, overweight and extremes of age. These authors have shown that the value for blood volume in either underweight or overweight individuals, though healthy, tends to deviate more from standard values when expressed according to body weight than when expressed according to body surface. In underweight persons the values per kilo of body weight tended to be high, and for those overweight the values were low.

By the use of the formula of Rowntree and Brown I have calculated the ideal total blood volume and have taken 42.4 per cent of it as ideal volume of red blood cells and 51.6 per cent as ideal plasma volume (3). These values have been converted into cc. per square meter of body surface and compared with the actual blood, plasma and red cell volumes per square meter.

The results of the determinations for pellagrins are shown graphically in figure 1. Data are shown in table 1 for 21 patients without pellagra, but showing varying degrees of anemia and undernutrition and some of them diarrhea. The outstanding features of the results are also stated in the summary below.

COMMENT

One of the mysterious features of pellagrous skin lesions is the difference in mechanism in severe skin damage which determines whether the lesion will take the wet or dry form. Severity of skin injury is not the explanation since some of the instances of most severe skin damage are those where mummification of the skin occurs. The dry form might be suspected of representing low capillary pressure and permeability and the wet form, high capillary pressure or permeability. Conceivably the magnitude of the circulatory blood volume might be an important part of the mechanism involved; high blood volume, possibly high plasma value, would promote exudation of plasma while low volume would oppose it. The work of Rous and Gilding (4) offers a strong basis for this concept. They have shown that when the blood volume of rabbits is greatly diminished by hemor-

VOLUME FOR 41 PELLAGRINS

ume and red cell volume are connected by vertical lines. Patients who died in the hospital indi-

rhage the blood supply to the viscera essential to life is little interfered with, while the skin and skeletal muscles suffer greatly and areas of

TABLE 1
Data concerning blood volume of 21 ward patients without pellegra
Standards for normal are same as used for pellagrins

Case number	[Percentile deviation from normal					Diagnosis
	Plasma volume	Red cell volume	Total blood volume	Weight	Red cell volume (Hematocrit)	
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	
1	+20	-75	-2	-20	-69	Severe pernicious anemia
	+29	-32	+4		-34	Remission
2	+6	-50	-21	-34	-41	Pernicious anemia or sprue. Mild diarrhea
3	+4	-27	-22	-20	-67	Severe hookworm anemia
4	+14	+22	+33	+11	-8	Hypertensive heart disease
5	-35	+43	-3	-23	+42	Acute fever. Dehydration
	-21	+25	-1	-23	+26	
6	+14	+9	+12	-9	-4	Probably early cancer of stomach
7	+20	-15	+5	-2	-21	Luetic periostitis
8	+14	-18	-0	-29	-21	Cancer of the lung
9	+44	-13	+20	-31	-28	Multiple myeloma
10	-13	+11	-2	-3	+14	Partial obstruction of cecum. Constipation. No vomiting
11	0	-14	-6	-16	-9	Chronic salpingitis
12	-10	+8	+2	-12	+12	Chronic salpingitis
13	-12	-50	-27	-33	-28	Severe pulmonary tuberculosis
	+5	-20	-6	-29	-16	Sprue. Chronic diarrhea
14	+8	-16	-1	-29	-13	
	-9	-26	-16	-29	-14	
15	+9	+12	+10	-26	-1	Mild diarrhea for 30 years
16	+18	-23	+2	-15	-26	Bacillary dysentery
17	-27	+24	-5	+5	+30	Diarrhea of unknown etiology
	-25	-19	-21	-15	-11	
18	-19	-29	-21		-11	Bacillary dysentery
	-17	-29	-27		-11	
19	0	+37	+16	-25	+16	Amebic dysentery
	-11	+30	+6	0	+19	
20	-9	-3	-6		+3	Severe diarrhea of unknown etiology
	-5	+5	+1		+2	
21	-11	-18	-14	-5	-17	Chronic diarrhea

ischemia develop in the skin and remain long after the blood volume has returned to normal. There is good clinical and postmortem evi-

dence to suggest that in chronic pellagra at least the skin may for a long time be deprived of adequate blood supply while actual engorgement of abdominal viscera is present.

Low blood volume may be a factor in the prevention of pellagrous dermatitis in the patients with pellagra sine pellagra. I have observations on a few such patients which are suggestive.

Unfortunately the data here reported offer little evidence bearing upon the part played by the magnitude of blood volume in the determination of the type of skin lesion. Only one patient (case 17) in the group studied showed the mummy-like lesions, which evolved during the period of study. His severe diarrhea and vomiting could not be controlled. Plasma volume showed great diminution at the time of the third study when the injured skin, previously red, had become dry, shrivelled and broken by deep fissures. Later, just before death, the plasma volume returned to its former level, due to administration of large quantities of fluids by hypodermoclysis. It will be noted that the cell volume by hematocrit does not fluctuate inversely as the plasma volume in accordance with the accepted idea. When plasma volume shrinks, one would expect cell volume to rise instead of fall. However, coincident fluctuations in serum proteins (5) are more closely correlated with the estimated plasma volume changes than are the cell volume changes.

The other patients with great variation from normal blood volume had such mild lesions that they could not be classified in either wet or dry group. Only the severe lesions show either marked exudation of serum or mummification. Study of patients before and after development of skin lesions is urgently needed. There is need of a uniformly reproducible experimental skin injury in connection with the study of pellagra. A clinical method for evaluating relative blood service to skin versus abdominal viscera is also needed.

It will be noted that some of the patients with lowest red cell volumes were those who had other diseases besides pellagra. This feature is discussed more fully elsewhere (5).

The blood volume findings for one patient (case 10) are of unusual interest. He had tuberculous peritonitis with fibrous matting of the intestines into large masses and also showed accumulations of ascitic fluid. A prolonged diarrhea probably due to partial intestinal obstruc-

tion preceded the development of pellagra. He had extensive dependent edema and dyspnea on exertion and his heart was enlarged. The blood picture was that of a profound anemia of the microcytic type. His plasma volume was enormous. His circulating red cell volume, though greater than the hematocrit reading would indicate, was still below normal. It seems likely that the circulatory inefficiency was due to the disparity between the great bulk of blood to be circulated, and the low concentration of the oxygen and CO₂ carrying element.

All the data for one patient (case 30) were exceptional. Clinically, he could hardly be called a sick man, the chemical findings were within normal limits, and both plasma and red cell volumes were above normal. He was a robust boiler-maker; though unemployed, he felt fit to work. For many years he had suffered from a gastric neurosis, and vomited following at least one meal each day. However, he had maintained his weight, strength and feeling of well-being almost perfectly. He had omitted lean meat from his diet. Unfortunately he was under observation for only 24 hours. His manifestations of pellagra were almost entirely cutaneous. Study of such exceptional cases should be of the greatest value due to the simplicity of the clinical picture. Observations on this patient are in keeping with the concept previously mentioned in the present series of papers, that many features of the disturbed physiology of pellagra appear to be caused by pellagrous injury to various body systems. These disturbances frequently cause their most definite symptoms after the diagnostic evidences of pellagra have passed.

Many of the patients who showed the lowest volume of circulating red cells were those who had low serum albumin (6) and were greatly underweight. It seems likely that both the low serum albumin concentration and anemia in pellagra may be due to malnutrition. A study of correlation between the two might indicate whether they were due to a common factor. Slight correlation¹ was found to exist between per cent deviation from normal serum albumin, and per cent deviation from ideal volume of red cells. The group of pellagrins studied contained several patients in whom pellagra was complicated

¹ $r = +0.339 \pm 0.007.$

by other diseases. The study of a larger group of patients with uncomplicated pellagra might be more enlightening.

It is well to remember that I have studied patients who were under excellent nursing care. If such studies were made on patients suffering from such neglect as many pellagrins receive in their homes, the results might be quite different.

SUMMARY

1. The results of 125 determinations by the dye method of circulating blood volume for 41 pellagrins are presented graphically.

2. Values for plasma volume, red cell volume and total blood volume are compared graphically with standards for normal as determined by the formula of Rowntree and Brown for underweight and overweight individuals.

3. Considering mean values for each patient expressed in terms of per cent deviation from ideal volume the results may be summarized as follows:

a. For 32 per cent of the group plasma volumes were above normal and for 68 per cent below normal. Plasma volume for 5 per cent of the patients showed a deviation of +21 per cent or greater; 15 per cent showed from +11 per cent to +20 per cent deviation; 12 per cent from +1 per cent to +10 per cent; 42 per cent of the patients showed deviation of from -1 per cent to -10 per cent; 10 per cent from -11 per cent to -20 per cent; 7 per cent showed from -21 per cent to -30 per cent; 7 per cent showed -31 per cent to -40 per cent; and 2 per cent showed deviation of greater than -40 per cent. The median was -4 per cent deviation.

b. Red cell volumes for 5 per cent of the pellagrins were above normal and for 95 per cent below normal. Ten per cent showed deviation of from -1 per cent to -10 per cent; 12 per cent showed -1 per cent to -20 per cent; 15 per cent showed -21 per cent to -30 per cent; 22 per cent showed from -31 per cent to -40 per cent; 22 per cent showed from -41 per cent to -50 per cent; 15 per cent showed from -51 per cent to -63 per cent deviation from normal standards. The median was -35 per cent deviation.

c. Total blood volumes for 17 per cent of the pellagrins were above ideal values and 82 per cent were below. Five per cent of the group

showed a deviation from ideal of +31 per cent or greater; 5 per cent showed from +11 per cent to +20 per cent deviation; 7 per cent from +1 per cent to +10 per cent; 17 per cent showed from -1 per cent to -10 per cent; 24 per cent showed from -11 per cent to -20 per cent; 24 per cent showed from -21 per cent to -30 per cent; and 17 per cent of the pellagrins showed a deviation of -31 per cent or greater. The median was -17 per cent deviation from ideal.

4. Data concerning blood volume for 21 patients without pellagra who showed various degrees of anemia, and malnutrition or diarrhea are presented in a table.

5. Anemic patients without pellagra showed plasma volumes higher than normal more frequently than those with pellagra.

6. A possible relationship between the magnitude of blood volume and the clinical features of severe skin lesions is discussed.

7. The plasma volumes of two pellagrins were persistently low for a long time even after the disappearance of any symptom which might explain low plasma volume.

8. There was slight positive correlation between the deviations from normal of serum albumin and of circulating red cell volume.

9. Individual cases of interest are discussed.

BIBLIOGRAPHY

1. Keith, N. M., Rowntree, L. G., and Geraghty, J. T., *Arch. Int. Med.*, 1915, xvi, 547. A Method for the Determination of Plasma and Blood Volume.
2. Rowntree, L. G., and Brown, G. E., *The Volume of the Blood and Plasma in Health and Disease*. Philadelphia, Saunders Co., 1929, p. 70.
3. Wintrobe, M. M., *Medicine*, 1930, ix, 224. The Erythrocyte in Man.
4. Rous, Peyton, and Gilding, H. P., *J. Exp. Med.*, 1929, l, 189. Studies of Tissue Maintenance. I. The Changes With Diminished Blood Bulk.
Gilding, H. P., *J. Exp. Med.*, 1929, l, 213. Studies of Tissue Maintenance. II. The Service to the Liver and Digestive Tract after Hemorrhage.
Gilding, H. P., and Rous, Peyton, *J. Exp. Med.*, 1929, l, 471. Studies of Tissue Maintenance. III. Persisting Bloodlessness After Functional Ischemia.
5. Guthrie, J. B., and Turner, R. H., *The Erythrocytes in Pellagra* (To be published).
6. Turner, R. H., *J. Clin. Invest.*, 1931, x, 71. The Pathologic Physiology of Pellagra. II. The Serum Albumin and Globulin.