FURTHER STUDIES ON THE CHEMISTRY OF BLOOD SERUM.*

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In a recent publication[1] the author recorded the results of a chemical analysis of blood sera from different diseased conditions. It was observed that the proteins of the serum are subject to extensive variations, and in certain diseases the globulin fraction in the serum is greatly increased. In the serum of cases of chronic parenchymatous nephritis the increase in the globulin content is most pronounced, and the globulin may constitute nearly all of the protein present. On the other hand, the protein fractions of sera from cases of chronic interstitial nephritis present, in their quantitative relations, little or no change from the normal. In certain cases of the latter group, there appears to be a tendency for the globulin in the serum to fall below the normal percentage.

For reasons which will be given in a future publication the author is of the opinion that the changes occurring in the protein composition of blood serum in different diseases are not accidental, but are the results of well defined influences acting upon the blood and its serum. In contrasting the findings in the sera of patients with chronic interstitial nephritis and with chronic parenchymatous nephritis, the conclusion is reached that the two diseases are genetically different in respect to the blood, and that the change in the protein composition of the blood serum plays a direct part in the production of some of the clinical manifestations of the two types of renal disease. The composition of the urine and the blood serum (the chlorides and nitrogenous waste products) in chronic interstitial nephritis depends upon the degree of impairment of the renal function; whereas in the chronic parenchymatous nephritis the chemistry

* This work was done under tenure of the George Blumenthal Jr. Fellowship in Pathology. Received for publication, January 21, 1913.

[1] Epstein, A. A., *Jour. Exper. Med.*, 1912, xvi, 719.

of the urine, the retention of fluid and salt in the body, and in a large measure the character of the disease in the kidneys, are due to changes occurring in the blood.

Since his last publication on the subject, the author has had the opportunity of examining a number of other blood sera from cases of genito-urinary disease. The particular object aimed at in the study of these cases was to ascertain to what extent localized renal affections react upon the composition of the blood, especially upon the protein content of the serum.

The cases studied are divisible into three groups. The first of these is comprised of minor surgical cases which may be regarded as normal. The second group consists of cases of hypertrophy of the prostate gland. Apart from the chronic interstitial nephritis found in many cases, this group is of interest because of the alleged effect upon the renal pathology and function of prostatic hypertrophy and the consequent retention of urine. The third series contains cases of localized renal affections, such as hydronephrosis, pyonephrosis, pyelonephritis, and nephrolithiasis. This group is important because the disease concerns the kidneys alone. Whatever changes arise in the composition of the blood can be definitely ascribed to disease of the kidneys.

Of the substances determined in the sera, mention will be made only of the total protein, of the incoagulable and non-protein nitrogen, and of the albumin and globulin contents.

The seven sera from the group of normal cases (table I) present values for the different substances which are in keeping with standard normal figures. The total protein in these sera ranges from 6.5 to 8.2 gm. per 100 c.c. of serum. The average of these figures amounts to 7.3 gm. The albumin present in all these sera is greater in amount than the globulin, which ranges from 2.1 to 3.2 gm. per 100 c.c. of serum, averaging 2.7 gm. per 100 c.c., or 37 per cent. of the total protein. In three sera the globulin content is somewhat higher than the average figure given; but in none does it rise above the quantity of albumin

The incoagulable and non-protein nitrogen in this group of sera is variable, ranging from 0.055 to 0.173 gm. of nitrogen per 100 c.c. of serum. This constituent, even in normal serum, is more variable than the relation of the albumin and globulin to the total protein. In two of the cases (M. C. and H. G.) duplicate analyses of the sera were made at intervals of a few days. The results are of interest in showing the variability of the incoagulable nitrogen and the constancy of the protein constituents of the serum.

TABLE I.[2]

Normal Cases.

Case.	Date.	Diagnosis.	Total protein.	Incoagulable nitrogen.	Albumin.	Globulin.	Per cent. of globulin.
M. C.	Nov. 21	Varicocele	7.169	0.070	4.544	2.625	36.6
M. C.	Nov. 24	Varicocele	7.175	0.057	4.744	2.431	34.0
S. L.	Nov. 7	Varicocele	7.319	0.094	4.800	2.519	34.4
H. S.	Oct. 1	Fistula	7.094	0.055	4.169	2.925	41.2
A. S.	Oct. 8	Perineal sinus	8.190	0.090	5.134	3.056	37.3
H. G.	Oct. 4	Hemorrhoids	7.675	0.072	4.450	3.225	42.0
H. G.	Sept. 29	Hemorrhoids	7.619	0.076			
J. A.	Oct. 7	Orchitis	6.969	0.107	4.844	2.125	30.5
S. S.	Sept. 15	Varicocele	6.481	0.173	2.531	2.950	45.7
		Average.....	7.300		4.404	2.72	37.7

TABLE II.

Prostatic Cases.

Case.	Date.	Diagnosis.	Total protein.	Incoagulable nitrogen.	Albumin.	Globulin.	Per cent. of globulin.
I. S.	Oct. 17	Hypertrophy	6.963	0.056	4.600	2.3637	33.9
H. S.	Oct. 29	Hypertrophy	7.294	0.079	4.541	2.753	37.7
I. Z.	Sept. 4	Hypertrophy	7.550	0.257	2.225	4.325	57.2
E. P.	Sept. 4	Hypertrophy	6.938	0.227	3.096	3.842	55.3
I. S.		Hypertrophy	5.887	0.114	2.900	2.917	49.5
S. G.	Nov. 19	Hypertrophy	6.894	0.067	3.969	2.925	47.7
A. W.	Nov. 25	Hypertrophy	7.787		4.510	3.275	41.4
A. L.	Oct. 4	Hypertrophy	7.531	0.055	4.194	3.337	44.3
A. L.	Oct. 29	Hypertrophy	7.469	0.080	3.869	3.600	48.0
M. R.	Oct. 8	Hypertrophy	7.225	0.154	3.600	3.625	49.0
M. R.	Oct. 11	Hypertrophy	6.750	0.125	3.338	3.412	51.0
		Average.....	?	?	?	?	41.6

[2] In tables I, II, and III the values are given in grams per 100 c.c. of serum.

Bladder Tumor.

M. W.	Sept. 22	Papillary carcinoma of bladder	6.756		3.181	3.575	
M. W.	Oct. 8	Papillary carcinoma of bladder	6.719		3.407	3.312	
H. P.	Oct. 15	Carcinoma of bladder and prostate	7.938	0.060	4.776	3.162	

In the second group (table II) eleven sera are from cases of prostatic hypertrophy, one is from a case of carcinoma of the bladder and prostate, and one from a papillary carcinoma of the bladder The protein content of this group of sera is almost normal in amount. The figures range from 5.887 to 7.551 gm. per 100 c.c. of serum. Three of the sera (from cases I. S., H. S., and H. P., table II) present also normal relations of the serum proteins. In the remaining sera the globulin content is above the normal amount, but the increase in the percentage of this protein is moderate.

Clinically all the cases of this group showed marked vascular and pulmonary changes. In two of the cases (E. P. and I. S.) there was a pronounced emphysema of the lungs, and in another (I. Z.) a diffuse purulent bronchitis was also present. Attention is called particularly to these clinical features, because, as pointed out in the previous communication,[3] the globulin content in the serum of such cases is usually above the normal amount. In the sera of the cases presented the globulin content averages 41.6 per cent. This moderate increase is not to be attributed to any alteration of the kidneys, but rather to the other conditions accompanying the renal changes; namely, emphysema, bronchitis, etc.

Duplicate analyses were made on the sera from two of the above cases (A. L. and M. R.). In one instance (A. L.) the blood specimens were withdrawn at an interval of twenty-five days; in the other case (M. R.) three days elapsed between the removal of the two specimens of blood. The findings show a slight fluctuation in the protein content of the sera.

The variation in the amount of incoagulable nitrogen of the sera of these cases is very great, but when compared with the urinary findings in the corresponding cases, it appears that the amount of incoagulable nitrogen varies with the degree of impairment of the renal function.[4]

The two cases of neoplasm of the bladder (M. W. and H. P.) present no noteworthy features. The serum of one of these (M. W.) was examined on two occasions separated by an interval of fourteen days; the results of the second examination do not differ from those of the first.

Of the group of six cases of localized renal affections (table III), twelve serum examinations were made. The findings illustrate the

[3] Epstein, A. A., *loc. cit.*

[4] The deductions drawn concerning the renal activity are based upon functional tests, the results of which will appear in a publication by Dr. Leo Buerger, Dr. Lautman, and the author.

point in question; namely, that disease of the kidneys proper does not affect the composition of the serum proteins.

TABLE III.

Localized Renal Affections.

Case.	Date.	Diagnosis.	Total protein.	Incoagulable nitrogen.	Albumin.	Globulin.	Per cent. of globulin.
L. G.	Sept. 10	Coincident hydropyonephrosis; horseshoe kidney	6.875	0.165	3.163	3.712	53.8
G. T.	Sept. 30	Hypertrophy of prostate	8.506	0.109	4.881	3.625	42.6
G. T.	Oct. 2	Renal calculi	7.606	0.093	4.156	3.450	45.2
G. T.	Oct. 14	Pyonephrosis	6.513	0.063	3.326	3.187	48.6
G. T.	Nov. 21	Perinephritic abscess	6.812	0.060	2.962	3.850	56.5
M. G.	Oct. 7	Double kidney	7.344	0.265	4.207	3.137	42.6
M. G.	Oct. 11	Hydronephrosis	7.312	0.011	4.356	2.956	40.4
T. B.	Aug. 31	Pyelonephritis	8.250	0.112	4.991	3.269	39.6
B. H.	Aug. 24	Pyelonephritis	8.125	0.149	3.038	5.087	62.6
B. H.	Aug. 30	Pyelonephritis	8.144	0.335	3.458	5.686	69.8
C. D.	Dec. 20	Unilateral tuberculosis of the kidney		0.065			
C. D.	Jan. 11		7.106	0.123	3.960	3.200	45.0

The cases referred to represent in the main pyogenic inflammations of the kidneys. To appreciate the net effect of such a process upon the blood serum it is necessary to consider, on the one hand, the effect of the infection upon the blood serum, and on the other, that of the destruction of kidney tissue and the impairment of the renal function.

Pathologically considered the infectious process in the kidneys is similar to that which may occur in any other part of the body. Its effect upon the chemical composition of the blood serum must be in all respects like that of a circumscribed infection or abscess formation in any other part of the body. As is well known, in all cases of pyogenic infection, but to a less extent in tuberculosis, the globulins in the blood serum are increased.[5] Thus we find in these cases that the globulin content in the serum is increased. The increase in the percentage relations of the globulin to the albumin and the total

[5] Erben, F., *Ztschr. f. klin. Med.*, 1903, l, 450.

protein appears to be proportionate to the duration and the extent of the infectious process. This inference, it seems, may be drawn from the results of the repeated examinations of the sera of two cases (B. H. and G. T.).

In the first case (B. H.) the blood serum was examined twice at an interval of six days. The clinical features in this case pointed to a rapidly progressing pyelonephritis. The chemical findings show that although the total protein in the serum remains constant, the globulin content rises from 62.6 per cent. to 69.8 per cent. The effect of the functional impairment arising from the destruction of renal tissue is manifested in the marked rise of incoagulable and non-protein nitrogen (from 0.149 to 0.335 gm. per 100 c.c. of serum).

In the second case (G. T.) the observations extended over a period of two months, and in all, four examinations of the blood serum were made. The clinical data in this case show that the disease progressed in two phases, one of which stands in relation to the protein composition of the serum, the other to the non-protein constituents of the serum. This patient had hypertrophy of the prostate, unilateral urethral and renal lithiasis, and pyonephrosis with a secondary perinephritic abscess, and in the course of the illness an extensive effusion on the chest developed. Disease in the second kidney was not demonstrable.

On the basis of what has been stated before, the results in this case show that the protein composition of the serum is affected by the pyogenic process, but is independent of the eliminatory function of the kidney; whereas the non-protein content is related to the activity of that organ.

It is seen from the figures in table III that the total protein in the serum falls progressively (8.506, 7.606, 6.513, and 6.812 grams per 100 c.c. of serum), and the amount of globulin remains constant; thus the percentage relation of the globulins to the total protein is progressively increased.

This result may be due to one or more of several causes: 1. A gradual increase in the globulin content with a progressive dilution of the blood (hydremia). The progressive loss of weight on the part of the patient argues against such an occurrence. 2. A greater loss of albumin than globulin in the purulent exudate discharged by the kidneys. The analyses of the urines made at different times show, however, that a greater loss of albumin in the pus could not account for the marked decrease in the total protein of the serum and the great rise in the percentage of globulin. 3. A greater loss of albumin in the serous effusion which occurred in the chest may

have contributed to the net result obtained. The total volume of fluid removed on aspiration of the chest amounted to 250 c.c. This fluid, unfortunately, was not submitted to chemical examination. 4. A greater destruction of serum albumin in the course of the protein metabolism in the body. This is a possible cause of the change observed in the composition of the serum, for the patient was kept for a long time on a diet rich in fats and carbohydrates but poor in proteins.

Table III shows that in this case the behavior of the non-protein nitrogenous substances is the inverse of that observed in the preceding case. The values drop gradually from 0.109 to 0.060 of a gram of nitrogen per 100 cubic centimeters of serum. This decrease becomes intelligible upon consideration of the clinical data. As stated above, the infectious process which originated in the kidney extended to the surrounding tissues, so that pus formation continued up to and beyond the time of the last serum examination. The effect of a pyogenic process upon the protein composition of serum has already been discussed. On the other hand, the renal function improved in consequence of surgical interference at the seat of disease. That an improvement in the renal function occurred was established by a study of the urine made at the same time that the different specimens of blood were examined. The fact that the patient was kept persistently on a low protein and high fat and carbohydrate diet may also have helped to reduce the non-protein nitrogenous bodies in the serum.

A third case of the same series (M. G.) shows even more strikingly the relation of the renal function to the non-protein composition of the serum, and the total lack of such relationship to the protein constituents. The two examinations of the blood serum were made four days apart; the first prior to, and the second after an operation upon the kidney. The results show that the protein content together with the relative amounts of albumin and globulin are within the normal range and remain constant. The non-protein nitrogen drops from 0.265 to 0.110 of a gram per 100 c.c. of serum. This result is in accord with the clinical developments of the case.

We have thus an indication of the twofold character of the chemical changes in the serum, resulting from localized disease of the

kidneys. The changes brought about by the infectious process affect the protein composition of the serum, whereas that which interferes with the renal function affects the nitrogenous waste products.

Another instance of the effect of the interference with the renal function upon the non-protein composition of the blood serum is found in the analysis of the serum of a case of unilateral renal tuberculosis (C. D.). In the first examination which was made prior to the operation upon the diseased kidney the amount of non-protein nitrogen in the serum was 0.065 of a gram per 100 c.c. After the removal of the diseased kidney this constituent of the serum rose to 0.123 gram per 100 c.c. Determinations of the urinary nitrogen made at the same time showed that the elimination of these substances after the operation was considerably less than that at the time of the first examination of the blood serum.

The other cases in this group show similar results. The nitrogenous waste products vary considerably in the different sera. The percentage of globulin is elevated in most of them, but this is attributable to the infectious process and not to any other cause with which the kidneys are functionally concerned. If we contrast the results obtained in these cases with those found in the sera of cases of chronic parenchymatous nephritis, reported in the communication already referred to, we find that in the case of localized renal affections the composition of the serum is entirely different. The globulin content in none of the latter cases reaches so high a level as that observed in the sera of parenchymatous nephritis.

SUMMARY.

The following conclusions may be drawn from the results obtained in this study.

1. In the minor surgical cases (considered normal) the chemical composition of the blood serum agrees, as far as its proteins are concerned, with the usual standard values. When examined at different times, the serum of such cases shows no variation in the total protein content or in its individual fractions. The incoagulable nitrogen, however, varies considerably in the total amount in the different cases, as well as in its percentage relations to the other constituents of the serum.

2. The cases of prostatic hypertrophy, with or without chronic interstitial nephritis, show no change from the normal in the character of the protein composition of the serum, nor in the ratio which the individual fractions bear to each other. On the other hand, the incoagulable and non-protein nitrogen of the serum show marked fluctuations, some of which correspond to the degree of functional deficiency of the kidneys.

3. In cases of localized infections of the kidneys, the changes in the blood serum are twofold. One concerns the proteins, and is traceable to the infection; and the other concerns the non-protein nitrogen, results from functional impairment, and varies with the amount of destruction of the kidney substance. Thus an increase in the globulins is observed in these sera similar to that occurring in infections in other localities; the non-protein content increases apparently in direct proportion to the degree of deficiency of the kidney, and becomes diminished when the function of the kidneys improves.

The author wishes to acknowledge his indebtedness to Dr. Leo Buerger for the privilege of studying the cases, and to Dr. Lautman, of the House Staff of Mount Sinai Hospital, for assistance in procuring the samples of blood.