STUDIES ON BLOOD SPECTRUM

III. APPLICATION OF BLOOD SPECTRUM TO CLINICAL DIAGNOSIS

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The usefulness of the blood spectrum as a tool for the appraisal of general condition and hepatic function has been studied in the preceding two papers of this series of research.[1,2] However, it seemed apparent that the items of examination involved in the graphs for the assessment of general condition and hepatic function were not always sufficient to establish the diagnosis of variegated diseases encountered in the daily practice of medicine and surgery. Most notable of the diseases which could not be sufficiently diagnosed by these were the maladies of kidney and pancreas. A supplemental graph composed of non-protein nitrogen, urea nitrogen and inorganic phosphorus in serum (graph of kidney function) was therefore introduced by *Shibata*[3] to improve the utilization of blood spectrum as well as to mend the above mentioned defect.

The present paper aims to describe, in the first place, the results obtained in the comparative study of the graph of kidney function and the blood urea clearance, and, secondly, to relate the application of the complete blood spectrum which comprises all of the graphs of general condition, hepatic function and kidney function to the diagnosis of important diseases.

METHOD

1. Graph of kidney function. Non-protein nitrogen (NPN), urea nitrogen (Urea N) and inorganic phosphorus (P) in serum were compared with blood urea clearance test of *Van Slyke*[4] on forty-nine to one hundred patients with and renal non-renal diseases. Cm (maximum blood urea clearance) and Cs (standard blood urea clearance) were expressed in the percentage of the standard values for the Japanese, namely of 70ml./min. and 50ml./min.,[5] respectively. NPN was determined by the digestion with mercury-salt containing sulfuric acid with direct nesslerization (*Shibata*, *Mizuta* and *Takahashi*,[6] urea N by the diacetyl-monoxime method (*Iuchi* and *Miyaji*),[7] and P by the colorimetric method of molybdate-aminonaphthol-sulfonic-acid (*Fiske* and *Subbarow*).[8] Normal values obtained by these procedure were 20-30 mg/dl (NPN), 8–15mg/dl (Urea N) and

2–5 mg/dl (P).

2. Application of blood spectrum to clinical diagnosis. Patients listed in Table I, numbering 2840, were examined for the complete blood spectrum;

TABLE I

Diseases of organ system as classified on the basis of the principal sites of illness.

Hepatobiliary organ	805
Digestive organ	484
Respiratory organ	325
Kidneys	288
Abdominal cavity excluding the liver and digestive tract	115
Endocrine organ	115
Circulatory organ	95
Blood	91
Skin	86
Central nervous system	85
Female genital organ	71
Muscle and subcutaneous tissue	51
Others	229
Total	2840 cases

graphs were made and classified according to the symbolization presented in the previous reports.[1-2] The graph of kidney function was constructed as shown in Figure 1, in marking the points of NPN, urea N and P placed separately on

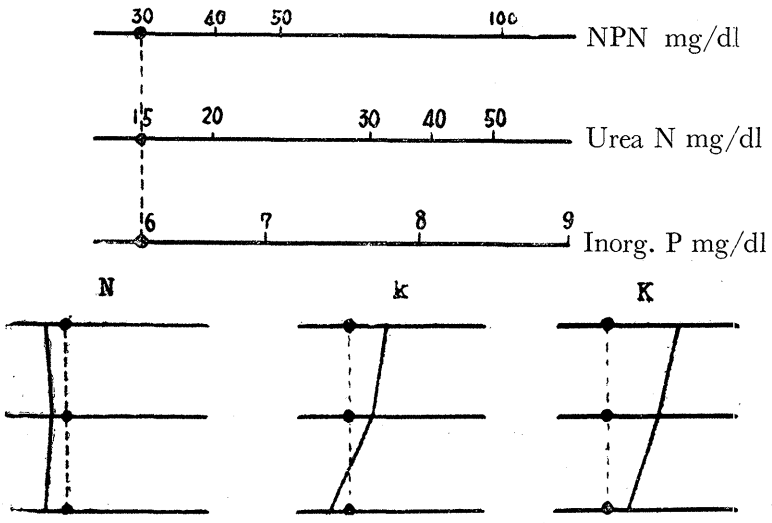
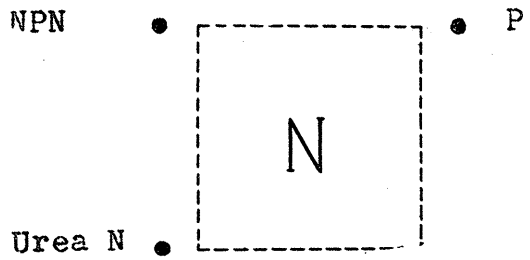


Fig. 1. Graph for the appraisal of kidney function and the patterns of the connecting lines.

the three parallel horizontal lines graduated from left to right according to the increase in their values. The upper limits of the normal range of the three chemical constituents were aligned on an imaginary rectilinear line which crossed vertically these horizontal lines. The lines which connected the points thus marked on the graduated lines were symbolized as follows: Pattern N for the connectiong lines in which none or one of the points lay to the right of the imaginary vertical line, pattern k for those in which two points were to the right of the vertical line, and pattern K for those in which all the points were right of this line. Dot (.) was affixed to the symbol N to indicate the relevant chemical constituent of supernormal concentration and accent (′) was appended to the symbol k to refer to the relevant constituent of normal (and subnormal) concentration. This allowed NPN, urea N and P to have the three corners (left shoulder, left foot and right shoulder) of the letter of symbol, respectively, as shown in Figure 2.



Examples: .N indicates the pattern in which urea N is increased over the upper limit of normal range, while NPN and P are normal or sunormal. k′refers to the pattern in which NPN and urea N supernormal, and P lies below the upper limit of normal range.

Fig. 2. The symbolization of the connecting line of the graph of kidney function with its examples.

Results

(I) *Graph of Kidney Function*

The comparison of NPN, urea N and P with the blood urea clearance test is presented in Figure 3. It will be apparent from the figure that there is a considerable discrepancy between them: if it is granted that the blood urea clearance which is below 50 per cent of standard value connotes the unequivocal renal dysfunction,[4] an appreciable number of renal disturbance exists without azotemia, and conversely, two thirds of the azotemic cases are unrelated to the obvious renal dysfunction. Direct translation of azotemia into the renal dysfunction will accordingly jeopardize the correct diagnosis and should be avoided. The same comment is also true with inorganic P in serum, even though Figure 3 discloses that the rise in P above 7 mg/dl is roughly associated with the kidney

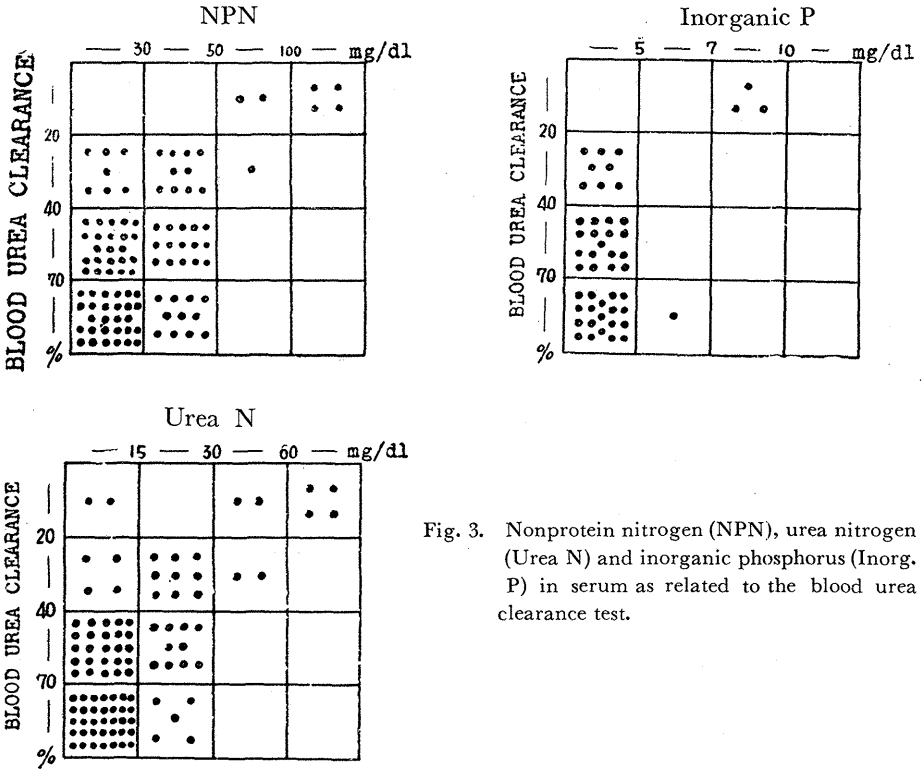


Fig. 3. Nonprotein nitrogen (NPN), urea nitrogen (Urea N) and inorganic phosphorus (Inorg. P) in serum as related to the blood urea clearance test.

disturbance. Increase in NPN, urea N and P is not infrequent in non-renal diseases, particularly in the case of severe hepatic diseases and dehydration (Figure 4). The ratio of urea N to NPN may be helpful to a certain extent in making the differential diagnosis of hepatic and renal azotemias, because this ratio (normal value: 0.5) tends to be below 0.5 in severe damage to hepatic parenchyma and it is frequently above the normal value in the case of renal disorders. However, it is necessary to adopt NPN, urea N and P as indicators of renal disturbance in spite of their demerits, because at present we have no other indicators which are superior to them.

(II) *Blood Spectrum of Important diseases*

Various patterns of blood spectrum were encountered according to the difference in the kind of diseases as well as in the severity of disorders, and some of the patterns were so peculiar and so characteristic of a special disease that they enabled us to directly make diagnosis even without reference to the record of morbid history. In the following, the symbolized average blood spectrums (symbols of the pattern of the graphs depicting general condition, damage to hepatic parenchyma, biliary obstruction and renal function as read from left to

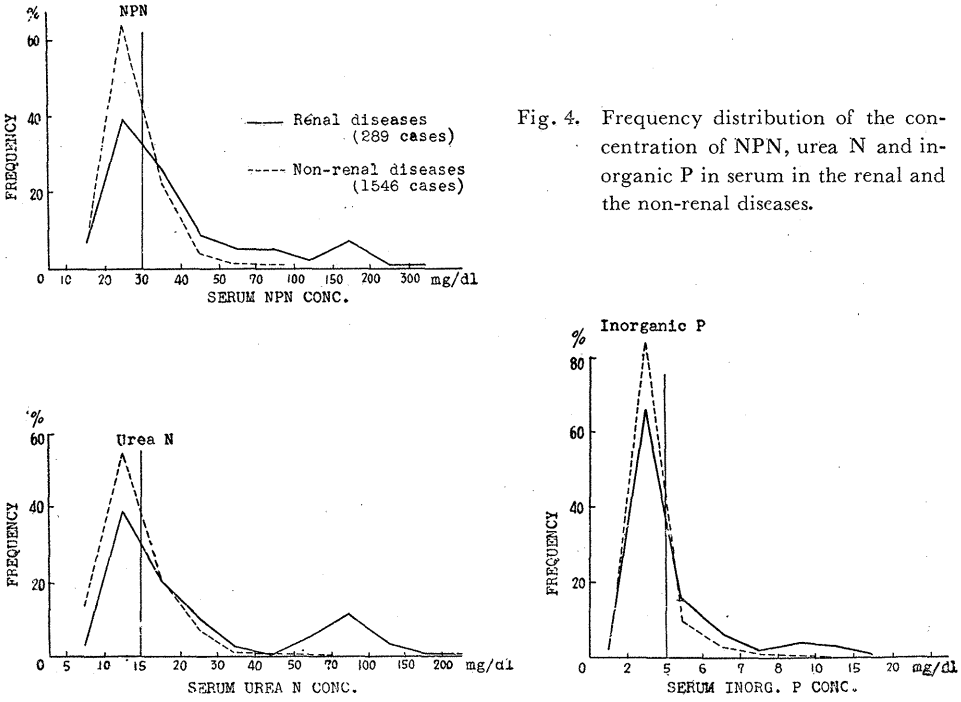


Fig. 4. Frequency distribution of the concentration of NPN, urea N and inorganic P in serum in the renal and the non-renal diseases.

right) of the important diseases will be presented in conjunction with their charts which depict the strips connecting the confidence limits ($\alpha = 0.05$) of each item comprising the relevant graphs.

1. Diseases of the kidney (Figures 5–11). The differential diagnosis of acute and chronic glomerulonephritides was possible to a certain exent, because the former disease was free of anemia, being Z ·n· N. .N in blood spectrum, in contrast to the presence of moderate anemia inherent in the latter disease which bore the pattern Z ·n· N. k′. Nephrolithiasis (Z ,d N. N) and kidney tuberculosis (Z N· N. N) resembled the glomerulonephritis. Nephrosis (lipoid) was quite different from the other renal diseases. Its blood spectrum F .n· n:k′ …… conspicuous hypoproteinemia associated with the marked decrease in serum albumin in combination with the remarkable increase in serum cholesterol, phenol turbidity test and serum cholinesterase …… was not common with any of the diseases, either renal or non-renal. The inspection of the blood spectrum has therefore never failed to give a correct diagnosis of nephrotic syndrome even in the absence of the aid of physical examination and of the record of morbid history. Kidney tumors Z D N. .N showed a damage to hepatic parenchyma, which was more prominent than in glomerulonephritides, and an anemia equaling in grade to chronic glomerulonephritis. The blood spectrum Z. D n: K of uremia was as characteristic as in the case of nephrosis. Striking increase in NPN, espe-

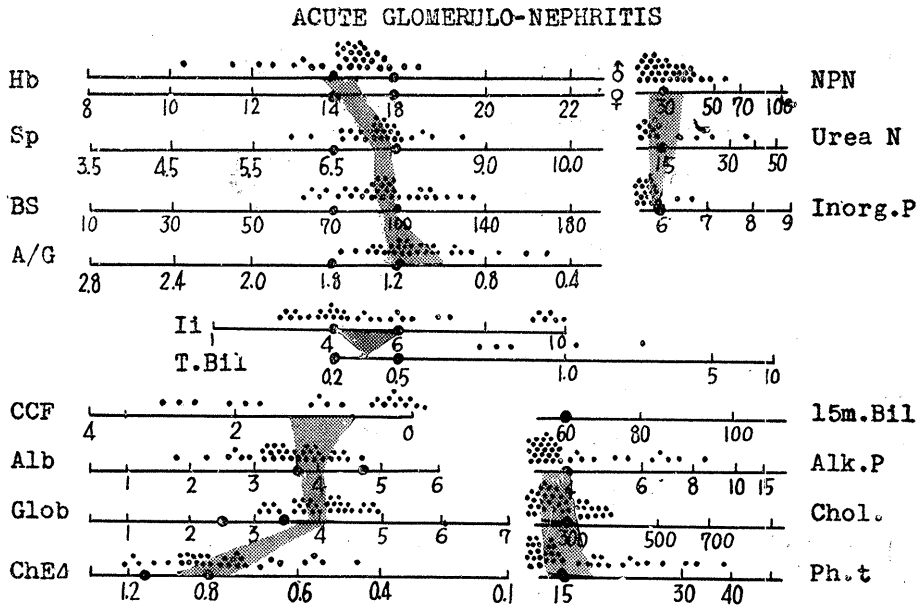


Fig. 5. Blood spectrum of acute glomerulo-nephritis.

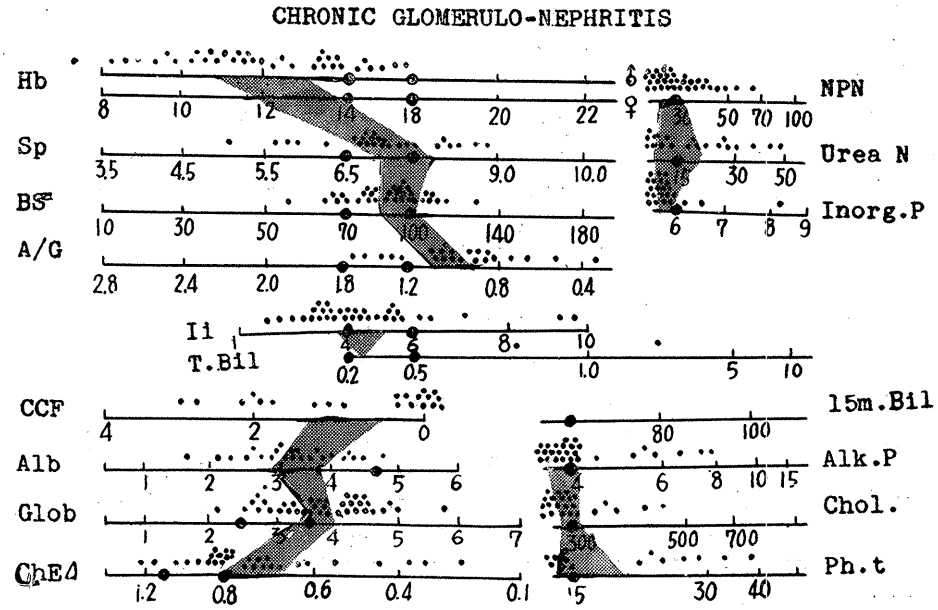


Fig. 6. Blood spectrum of chronic glomerulo-nephritis.

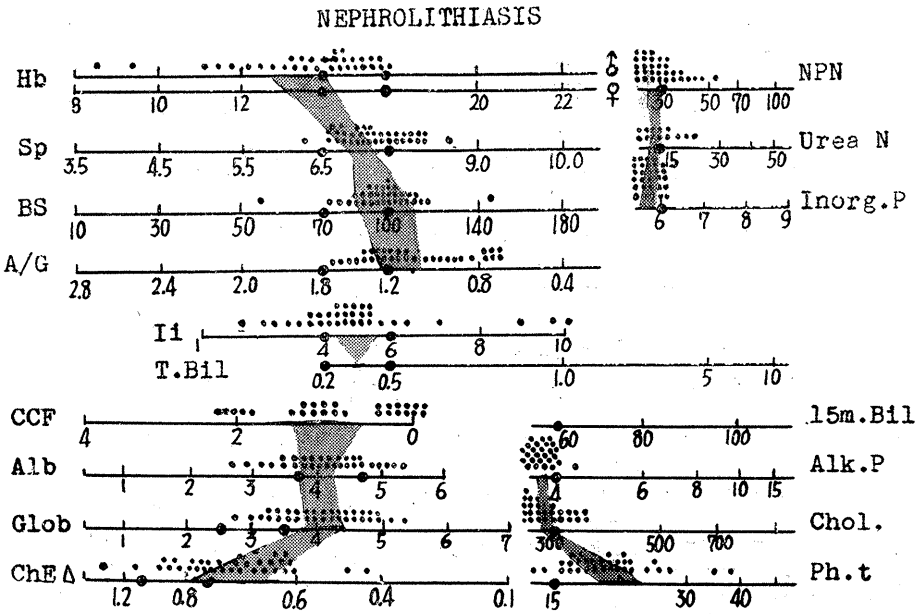


Fig. 7. Blood spectrum of nephrolithiasis.

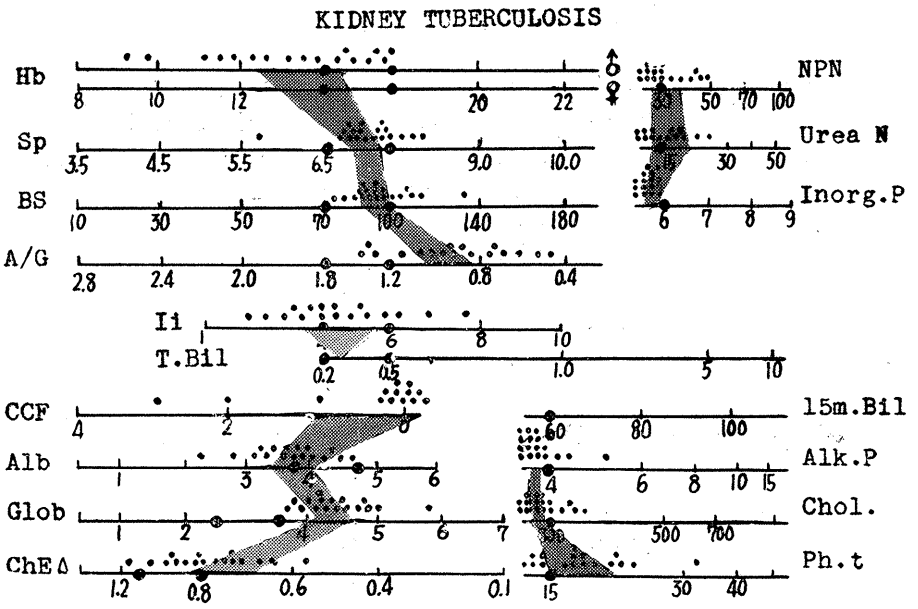


Fig. 8. Blood spectrum of kidney tuberculosis.

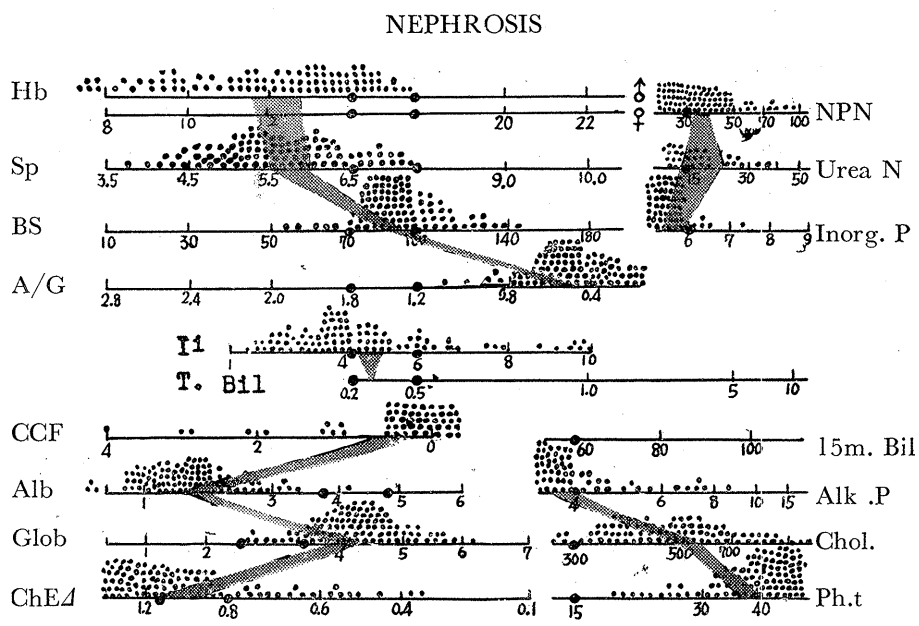


Fig. 9. Blood spectrum of nephrosis.

cially in urea N, phosphatemia and hyperglycemia in association with profound anemia and the diminution of serum cholinesterase activity permitted the diagnosis of uremia with highest certainty.

2. Diseases of circulatory organs (Figures 12 and 13.) In essential hypertension (Figure 12) there was little impairment in general condition and hepatic function. Its blood spectrum L N· n: .N was not so remarkable as that of glomerulonephritis, being free of azotemia apart from the occasional incident of slight increase in urea N. Figure 13 represents our collection of the cases of circulatory failure (L 'd N N).

3. Diseases of respiratory organs (Figures 14-20). In pulmonary tuberculosis which was unaccompanied by the tuberculous or other complication of extra-pulmonic organs there was increasingly evident deviation of blood spectrum from its normal pattern with the spread of the pulmonary lesion as examined radiologically: N N N N, L ·n· N N and Z D .N N in mild (pulmonary lesion up to 1/3 of total bilateral pulmonary areas), moderate (pulmonary lesion narrower than 2/3 of bilateral pulmonary areas), and advanced (pulmonary lesion wider than 2/3 of bilateral pulmonary areas) cases, respectively. Exudative pleurisy Z D N N was nearly equal in blood spectrum to advanced pulmonary tuberculosis. A more remarkable distortion of blood spectrum was encountered in pneumonia (ZDNN), pulmonary abscess (Z.DNN) and pulmonary cancer (ZDN.N), but their differential diagnosis was difficult on account of their similarity in pattern.

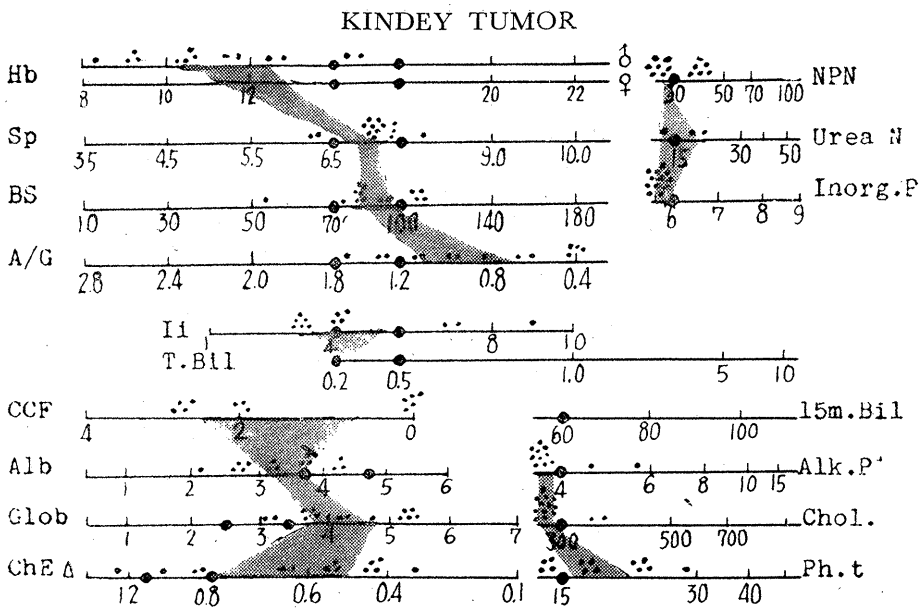


Fig. 10. Blood spectrum of kidney tumor.

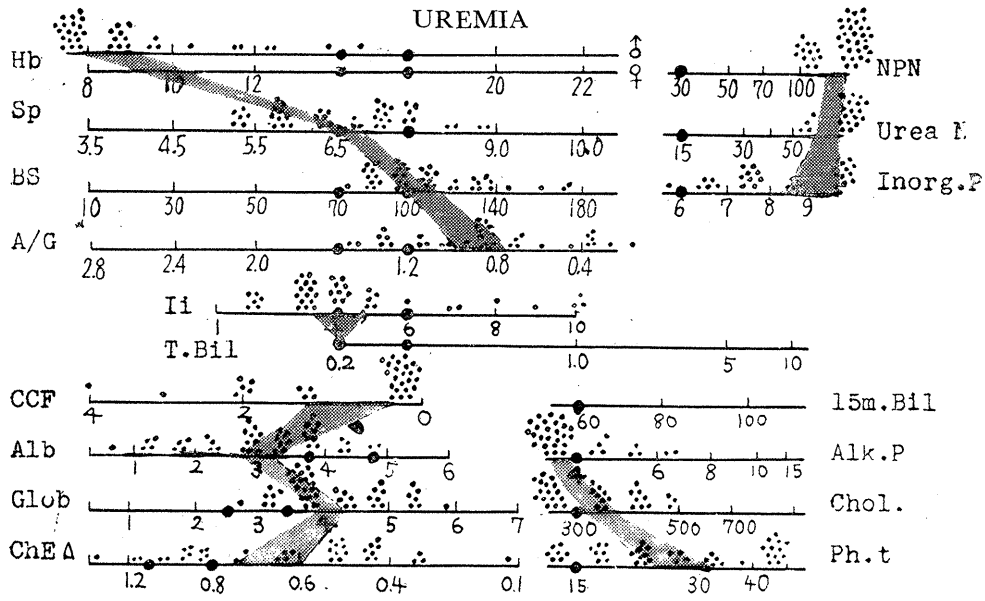


Fig. 11. Blood spectrum of uremia.

ESSENTIAL HYPERTENSION

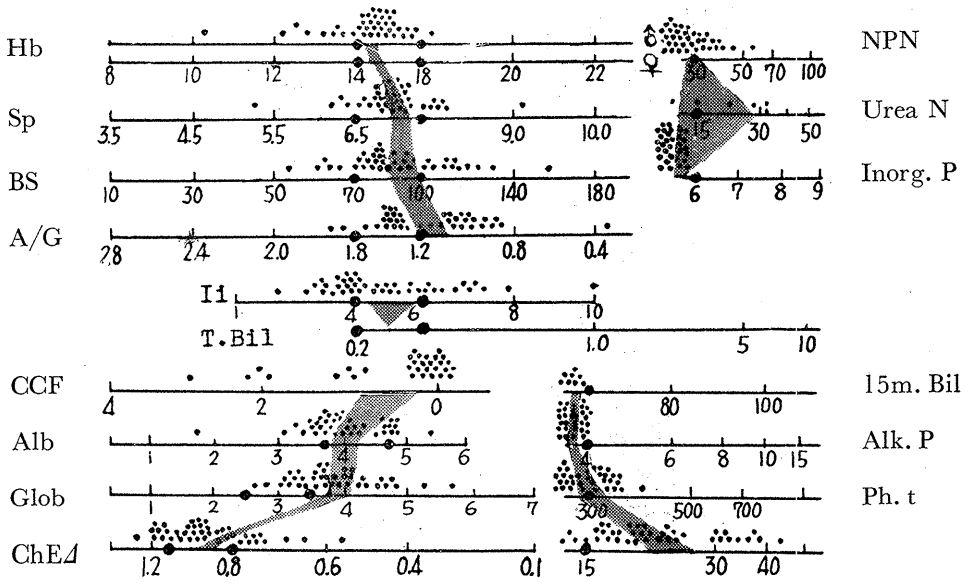


Fig. 12. Blood spectrum of essential hypertension.

CIRCULATORY FAILURE

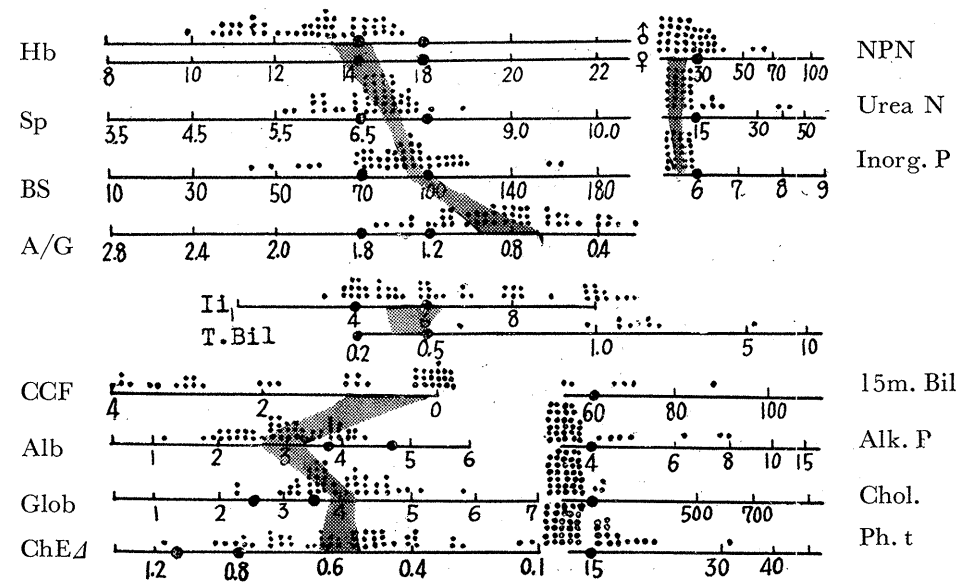


Fig. 13. Blood spectrum of circulatory failure.

MILD PULMONARY TUBERCULOSIS

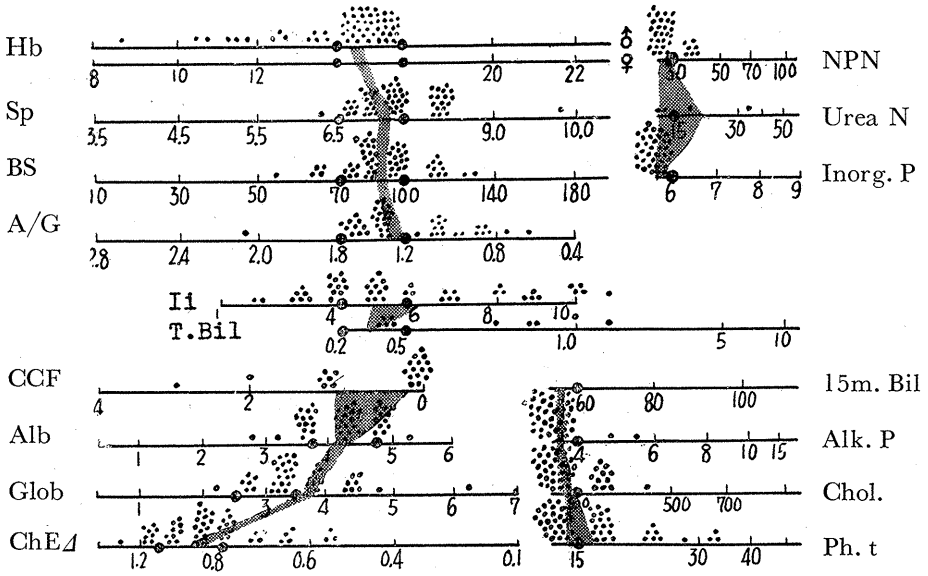


Fig. 14. Blood spectrum of mild pulmonary tuberculosis.

MODERATE PULMONARY TUBERCULOSIS

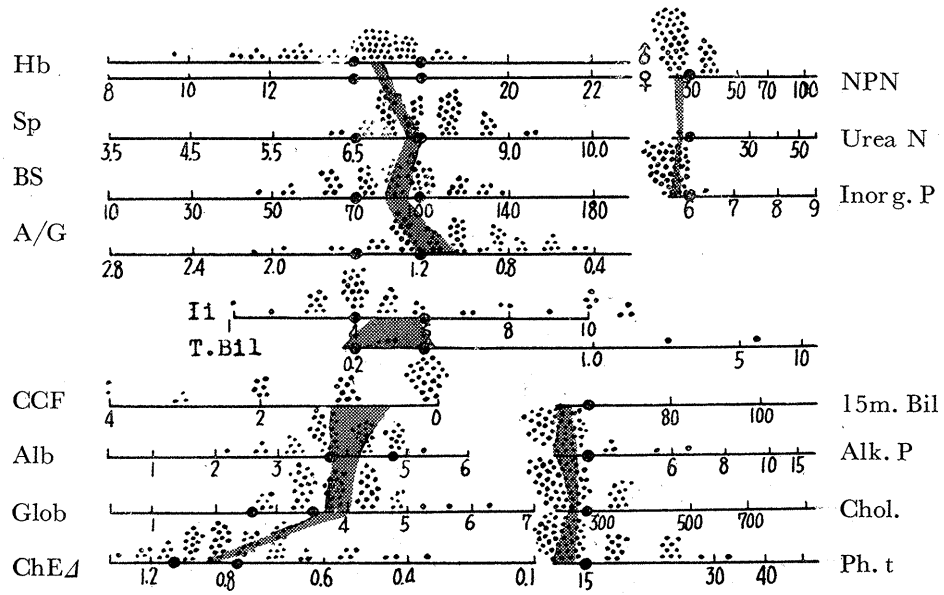


Fig. 15. Blood spectrum of moderate pulmonary tuberculosis.

ADVANCED PULMONARY TUBERCULOSIS

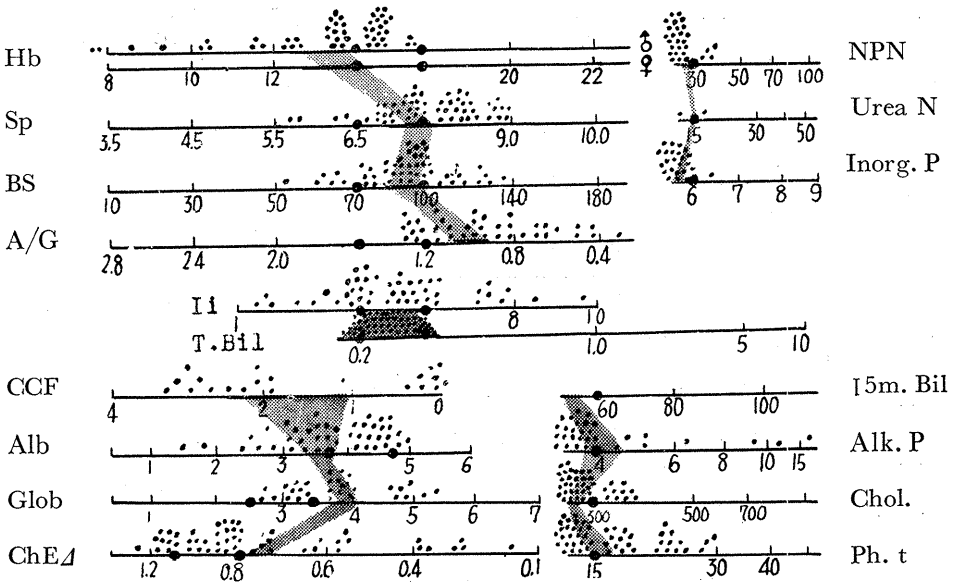


Fig. 16. Blood spectrum of advanced pulmonary tuberculosis.

PLEURISY

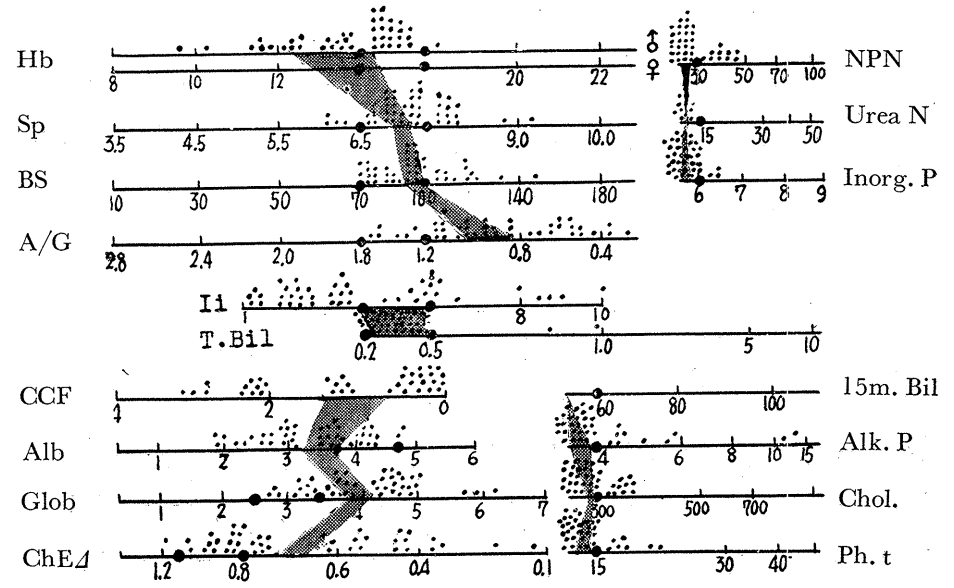


Fig. 17. Blood spectrum of pleurisy.

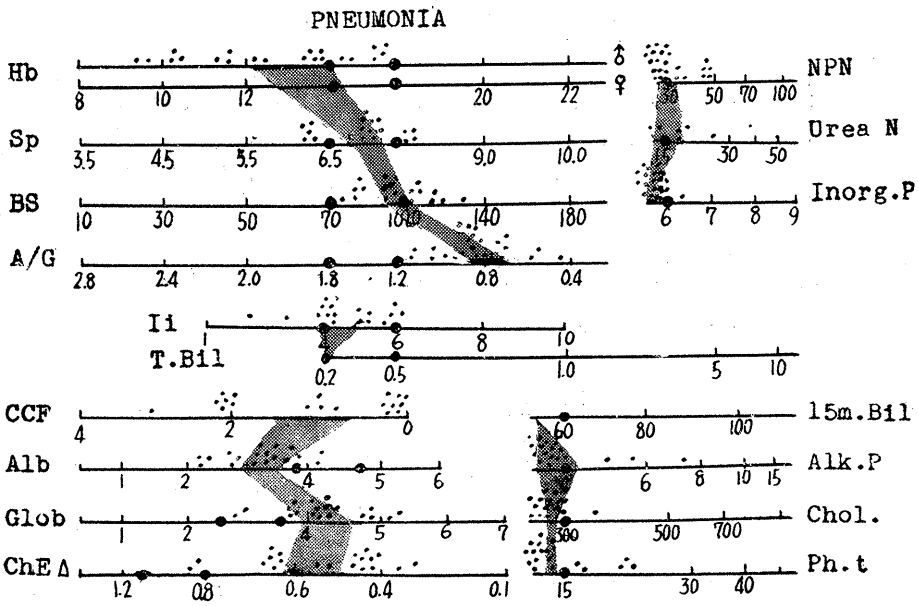


Fig. 18. Blood spectrum of pneumonia.

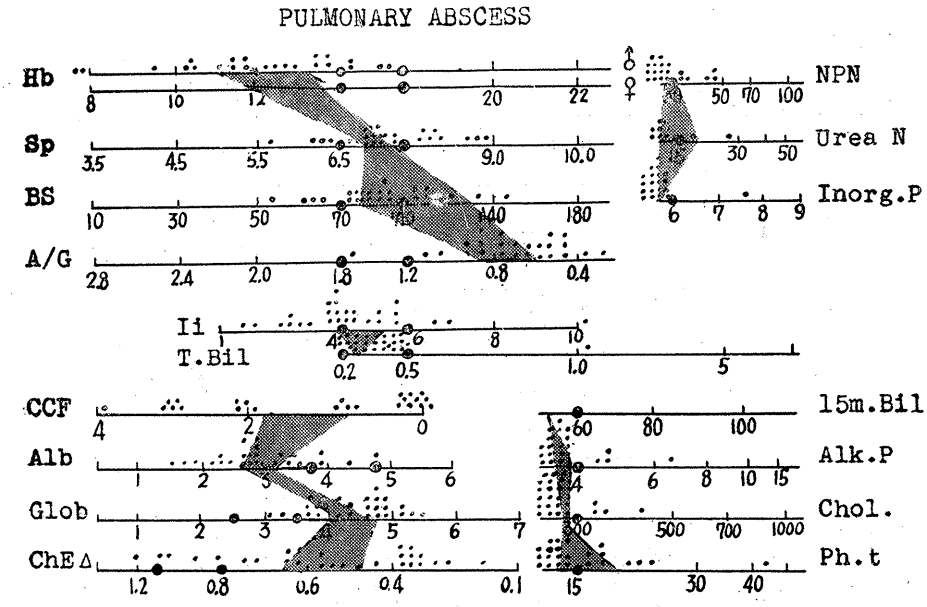


Fig. 19. Blood spectrum of pulmonary abscess.

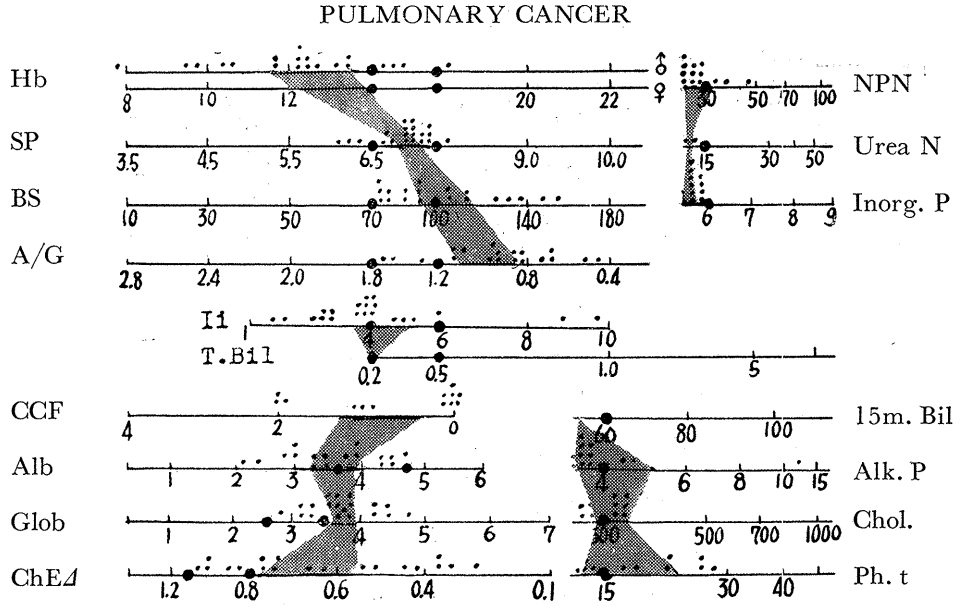


Fig. 20. Blood spectrum of pulmonary cancer.

4. Blood diseases (Figures 21–23). Hypochromic microcytic anemia (MCC $<32\%$) Z n: N N and anemia of ankylostomiasis Z 'd N N showed profound anemia and hepatic dysfunction, but the damage to hepatic parenchyma was more evident in the latter. Myeloid leukemia Z(i?) D .N .N was characterized by the increase in alkaline phosphatase activity and severe impairment in hepatic function as well as in general condition. Blood spectrum was generally useful to pursue the variation of anemia during the course of blood diseases.

5. Endocrine diseases (Figure 24). Diabetes mellitus was the sole disease among the endocrine disorders for which we could collect, statistically, a significant number of cases. Hyperglycemia associated with slight lipemia was so characteristic of its spectrum L. 'n' n: N that it was easily diagnosed.

6. Diseases of digestive organs (Figures 25 and 26). The differential diagnosis of gastroduodenal ulcer 'N N. N N and gastric cancer Z .n. N N was possible to some extent because anemia was generally the only one abnormal finding in the former, although the latter was commonly attended by a considerable impairment in general condition and decrease in serum cholinesterase activity.

7. Hepatobiliary diseases. Infectious hepatitis (Figures 27–31):– Acute and subacute yellow atrophy of the liver Z. (i) D .N 'N was distinguished from the ordinary cases of infectious hepatitis by the extreme alteration in blood chemistry, such as severeness in jaundice and anemia, strongly positive CCF, marked

HYPOCHROMIC MICROCYTIC ANEMIA

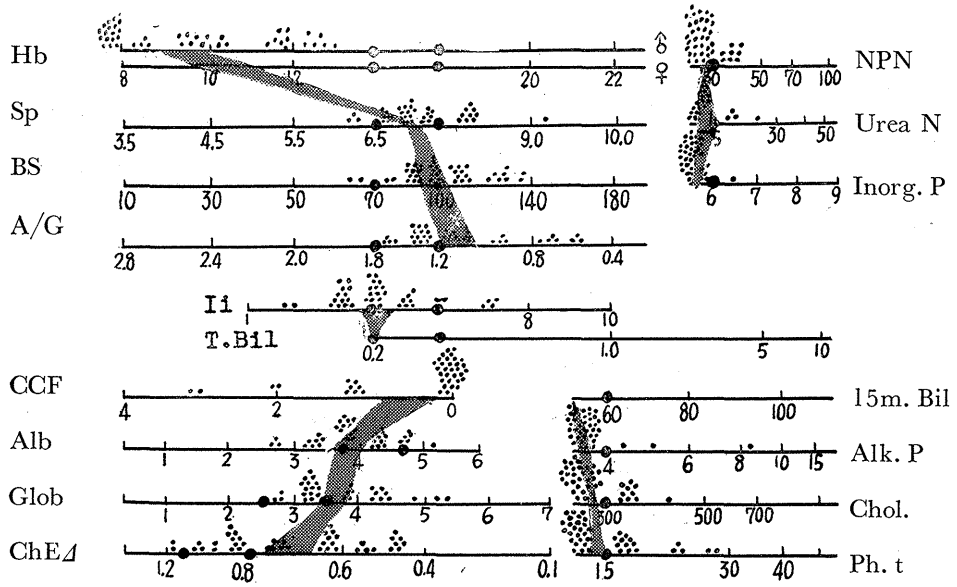


Fig. 21. Blood spectrum of hypochromic microcytic anemia.

ANKYLOSTOMIASIS

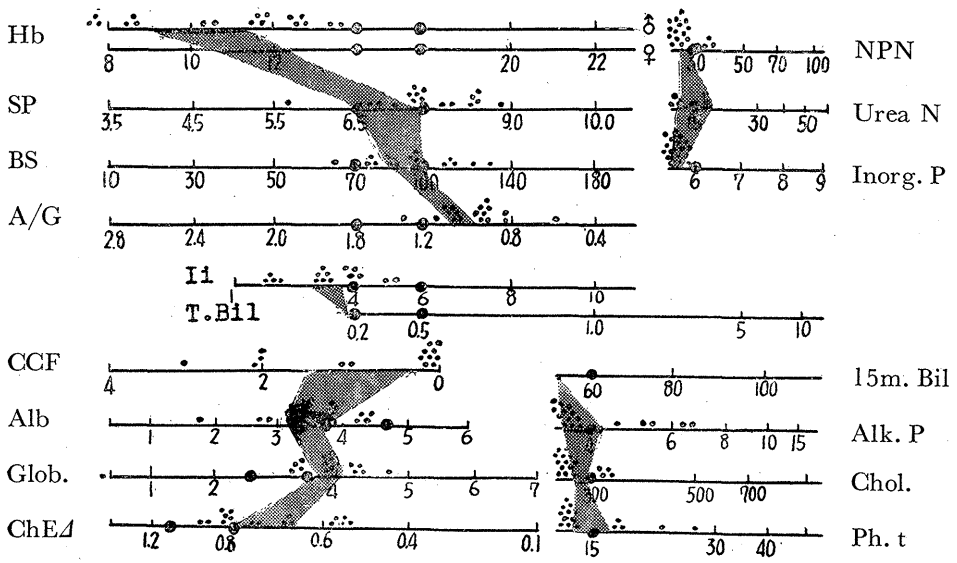


Fig. 22. Blood spectrum of ankylostomiasis.

MYELOID LEUKEMIA

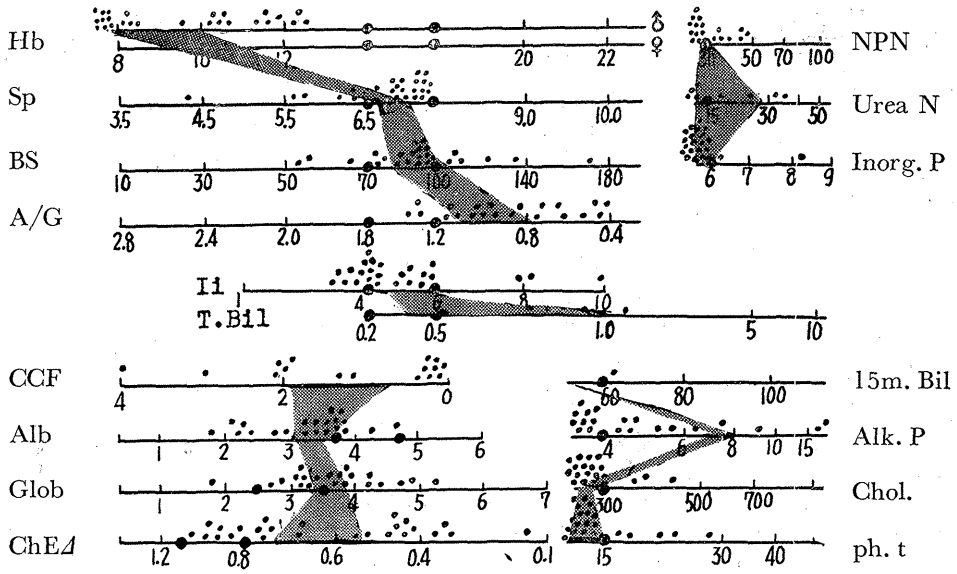


Fig. 23. Blood spectrum of myeloid leukemia.

DIABETES MELLITUS

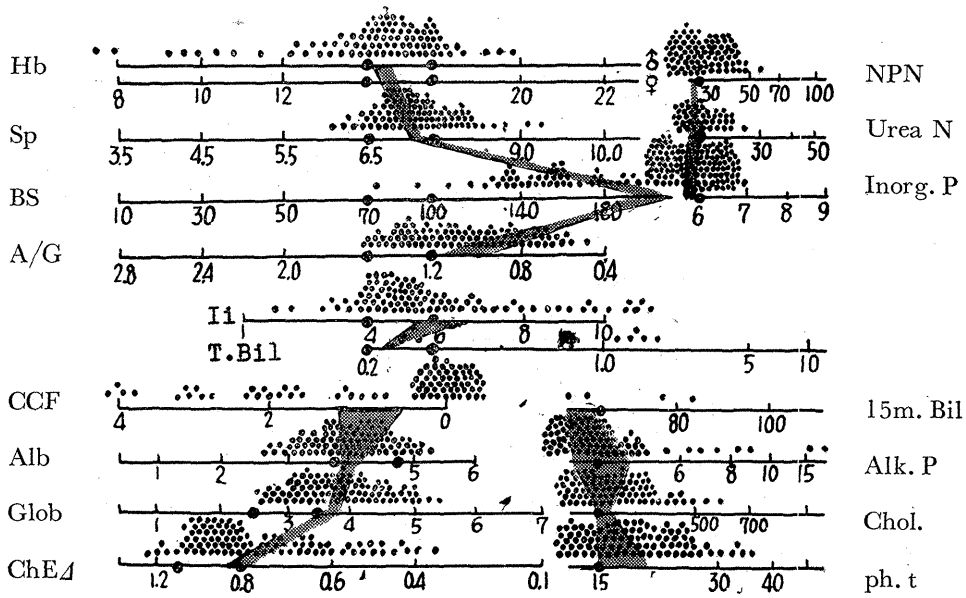


Fig. 24. Blood spectrum of diabetes mellitus.

GASTRODUODNAL ULCER

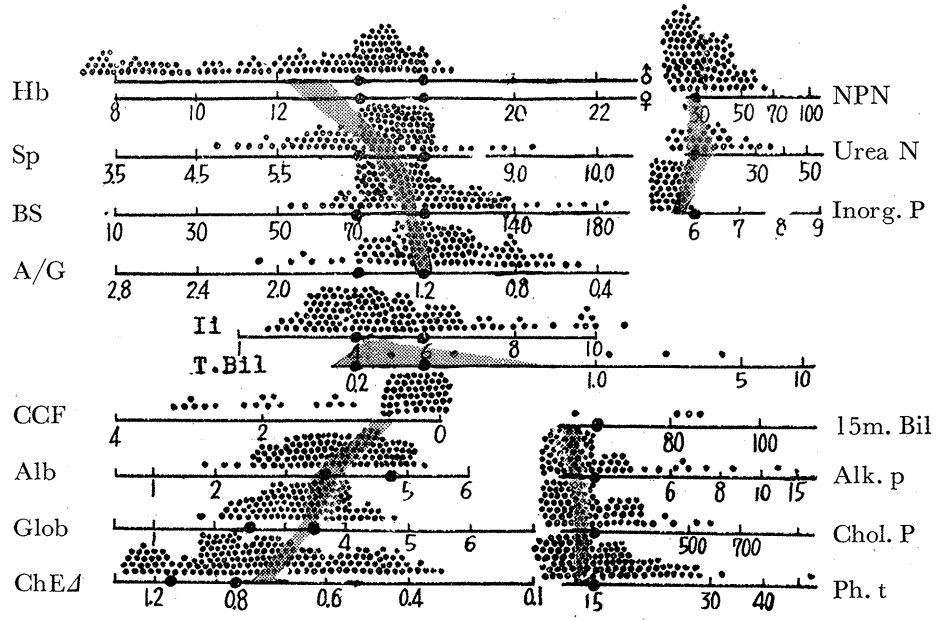


Fig. 25. Blood spectrum of gastroduodenal ulcer.

GASTRIC CANCER

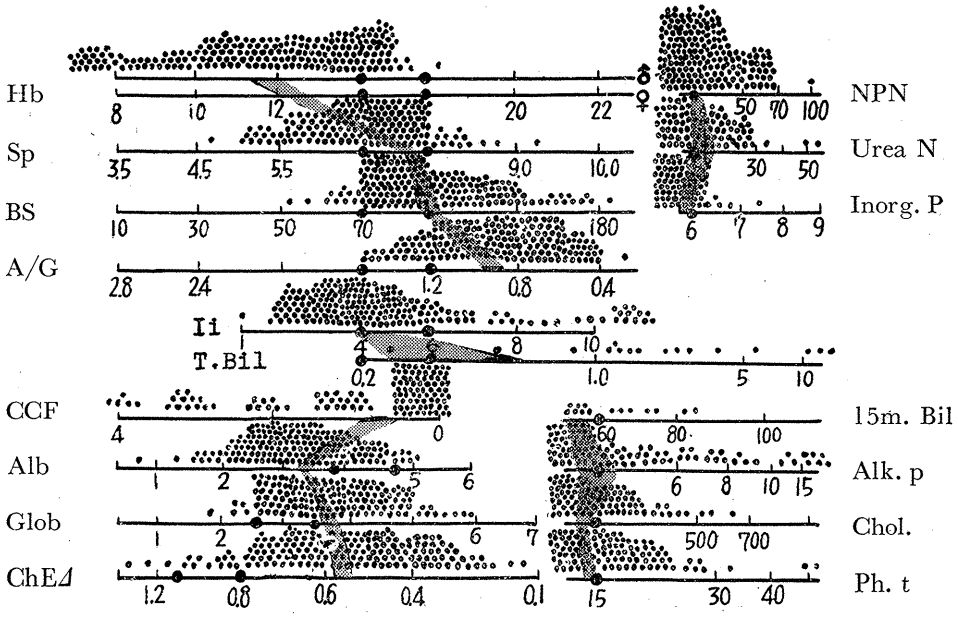


Fig. 26. Blood spectrum of gastric cancer.

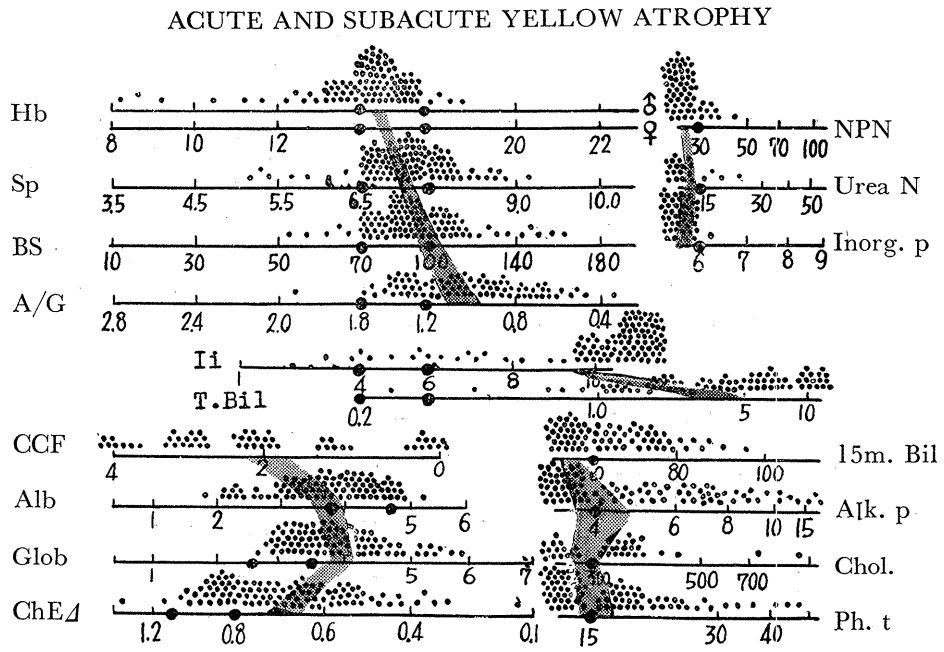


Fig. 27. Blood spectrum of acute and subacute yellow atrophy of the liver.

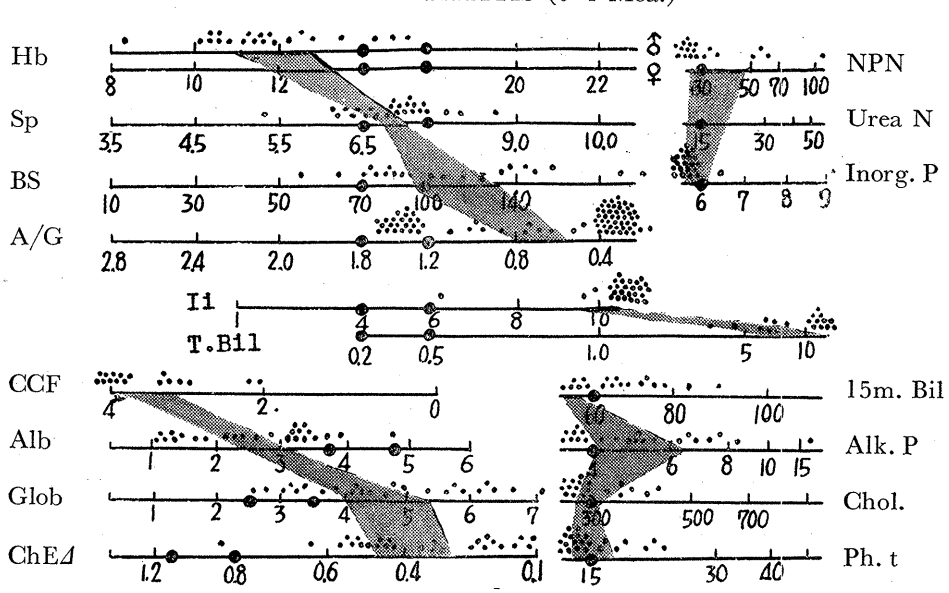


Fig. 28. Blood spectrum of acute hepatitis (0–1 Mon.)

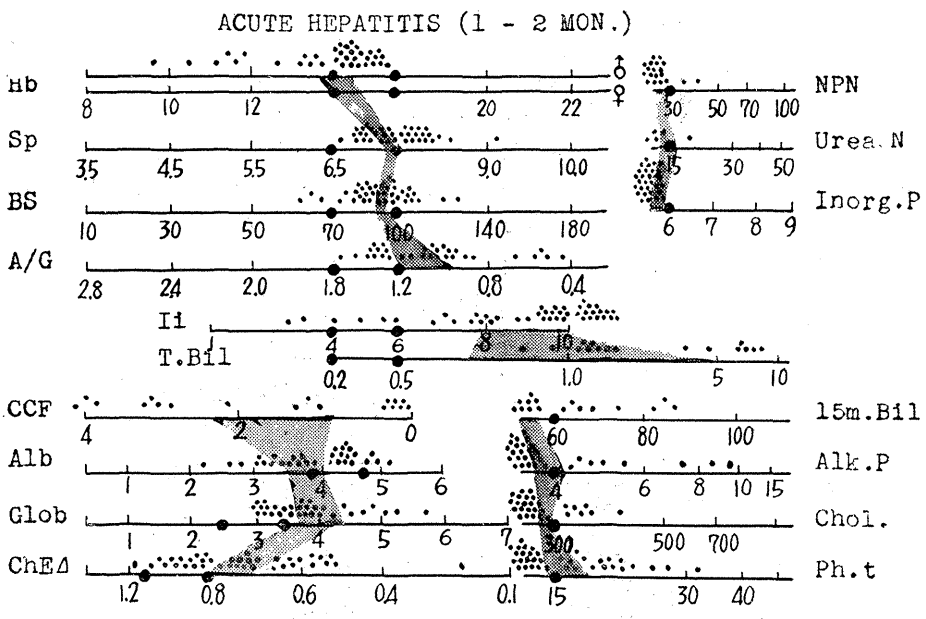


Fig. 29. Blood spectrum of acute hepatitis (1–2 Mon.)

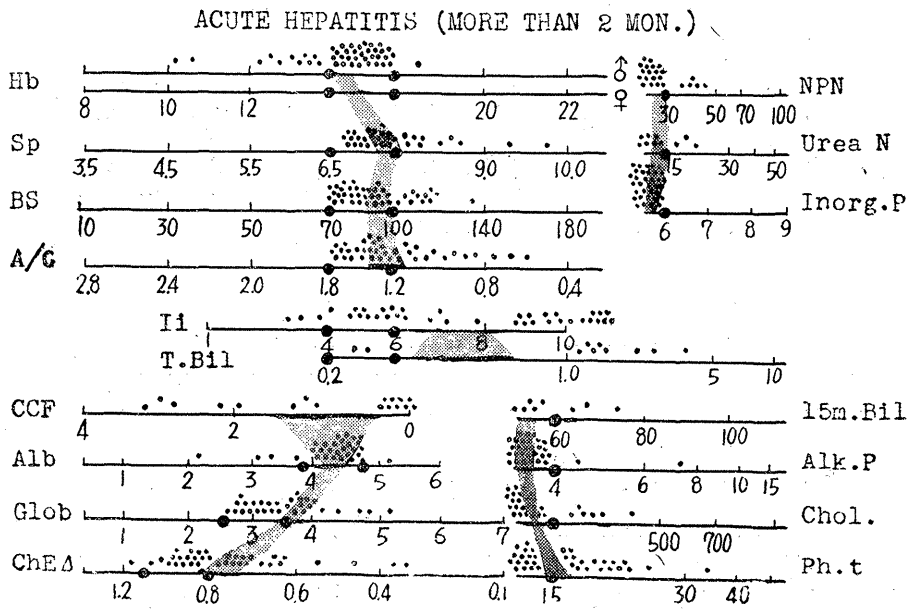


Fig. 30. Blood spectrum of acute hepatitis (more than 2 mon.)

reduction of serum cholinesterase activity and azotemia. In infectious hepatitis the blood chemistry was very remarkably changed in the first morbid month to (L (i) ,d N N). In the second month the change was less conspicuous, being (L (i) ·n· N N), and it was restored almost completely to the normal pattern of (N (i) ·N N N) at the end of more than two months. However, a hepatic disturbance of the grade slighter than that in the first month was persistent in the cases which passed into the chronic stage (L (i) ·n. N N).

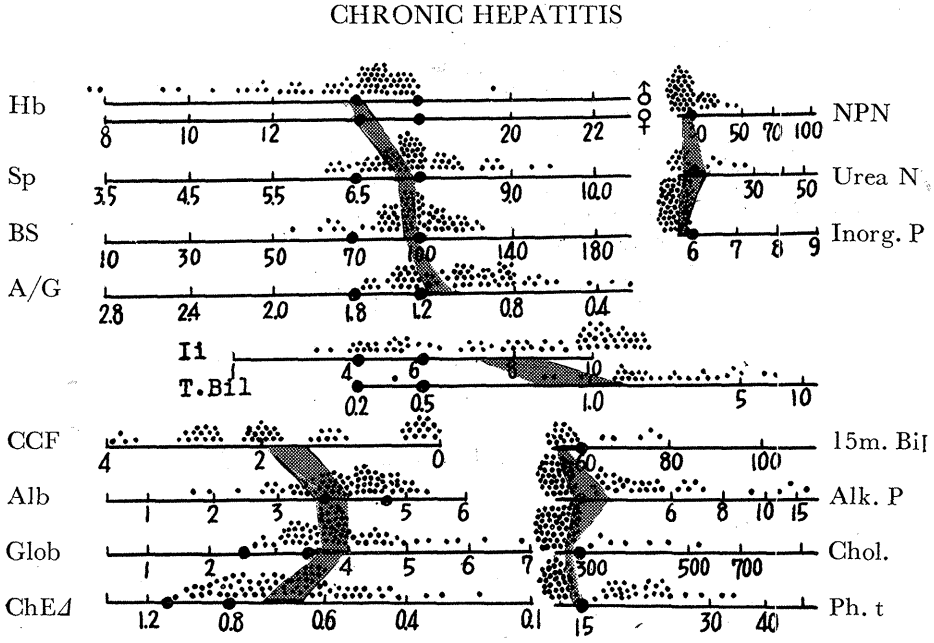


Fig. 31. Blood spectrum of chronic hepatitis.

Liver cirrhosis (Figures 32–34):– Portal cirrhosis (Z (i) D .N N) and biliary cirrhosis (Z. (i) D O k') formed the disease entities which were relatively easy to discriminate from the common cases of infectious hepatitis because of the profound disturbance in hepatic function. Little difficulty was experienced in the differentiation of biliary cirrhosis from the portal cirrhosis because of the notable indication of biliary obstruction in the former disease. Incidentally, acute and subacute atrophy of the liver exceeded the portal cirrhosis in the intensity of jaundice, while it was behind the biliary cirrhosis in the sign of the obstruction to biliary outflow. Banti's syndrome (Z(i) D N N) was distinguished from the typical case of portal cirrhosis by the comparative slightness in the damage to hepatic parenchyma.

PORTAL CIRRHOSIS

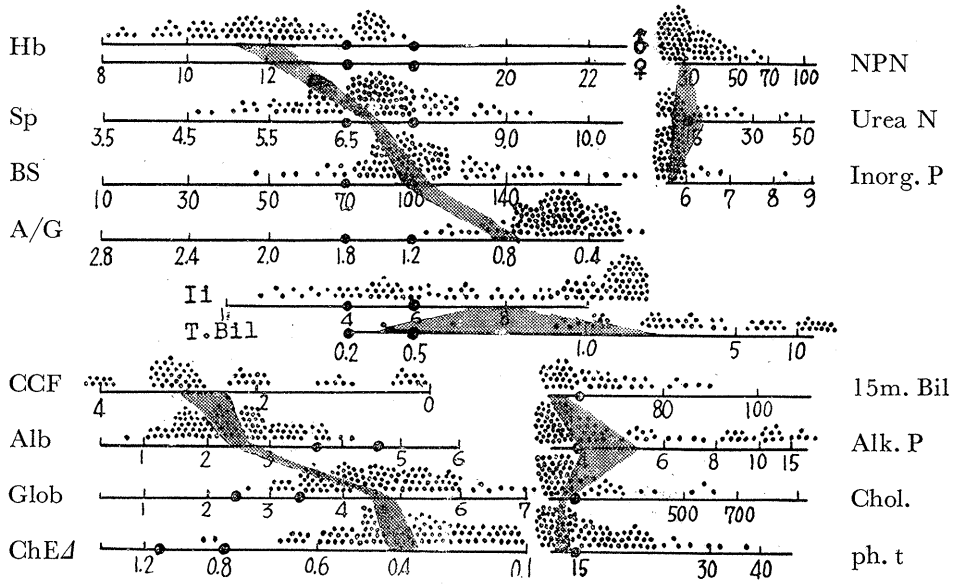


Fig. 32. Blood spectrum of portal cirrhosis of the liver.

BILIARY CIRRHOSIS

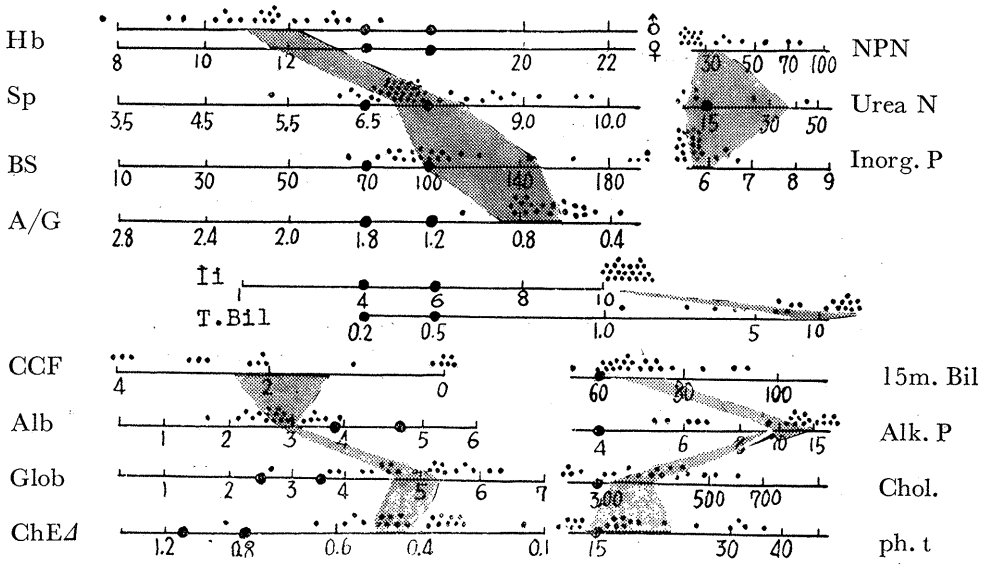


Fig. 33. Blood spectrum of biliary cirrhosis of the liver.

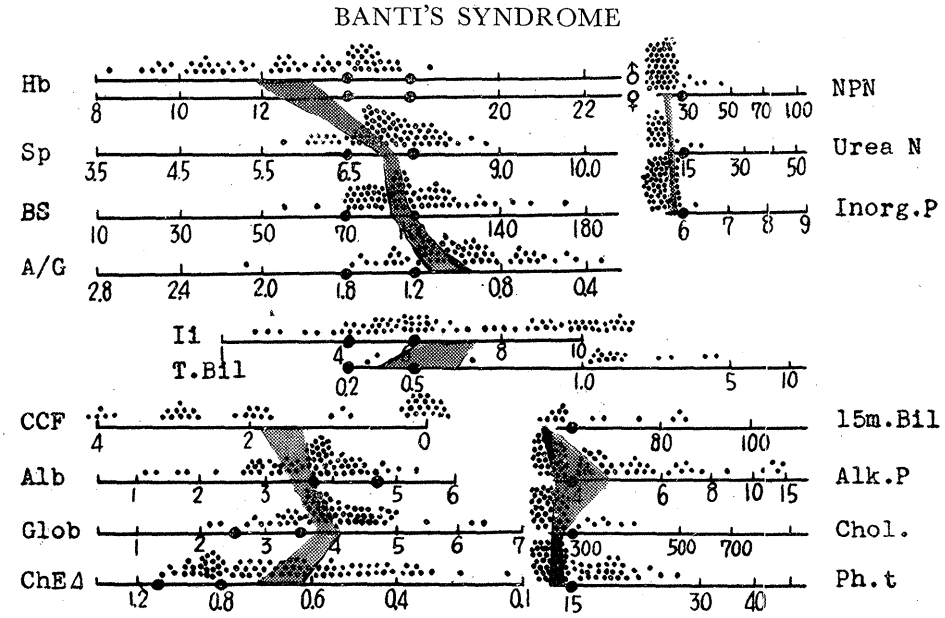


Fig. 34. Blood spectrum of Benti's syndrome.

Liver abscess and liver cancer (Figure 35 and 36):– Liver abscess and liver cancer were characterized by the hepatic dysfunction and the increased activity of serum alkaline phosphatase which were more evident than in the case of Banti's

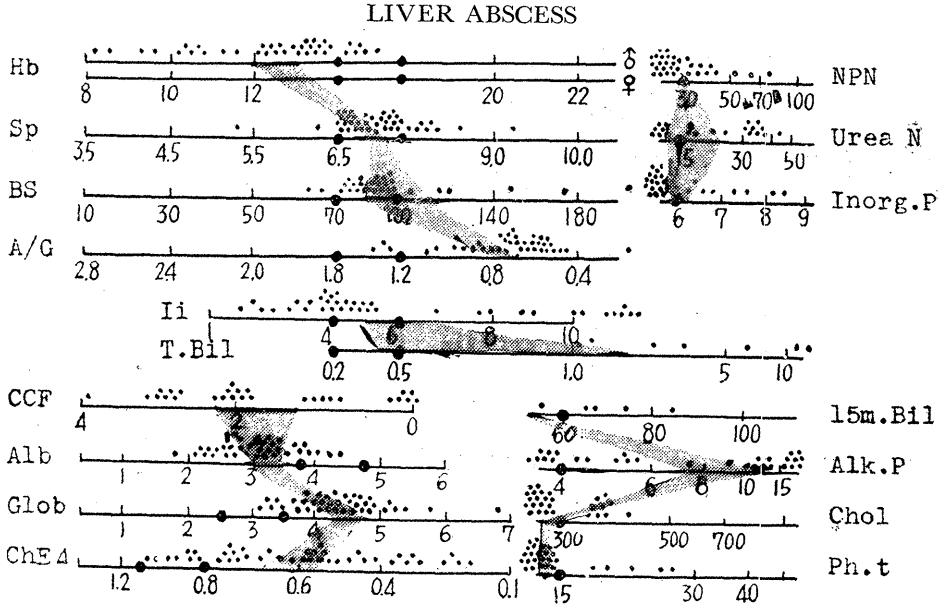


Fig. 35. Blood spectrum of liver abscess.

syndrome. However, the differential diagnosis of these diseases by blood spectrum (Z (i?) D .N N) was impossible.

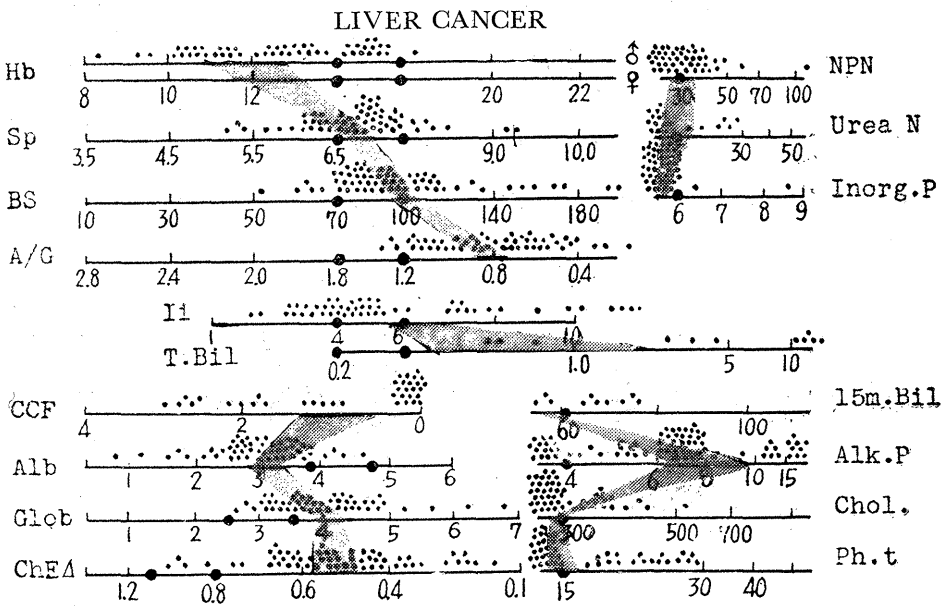


Fig. 36. Blood spectrum of liver cancer.

Benign and malignamt biliary obstruction (Figures 37 and 38):– Both damage to hepatic parenchyma and disturbance in biliary outflow were less evident in benign biliary obstruction Z (i) ,d .N N than in malignant biliary obstruction Z. (i) D O N. Blood spectrum contributed therefore to the differential diagnosis of these diseases to a certain extent. Apart from the faintly positive CCF, the malignant obstruction resembled closely the liver abscess and the liver cancer.

Discussion

According to *Kaneko*,[5] the azotemia did not make its appearance as long as the kidney function remained above the level of 35 per cent of the normal blood urea clearance, and only the kidney dysfunction below 20 per cent of normal level, as measured by the blood urea clerance test, was responsible for the constant increase in NPN and urea N. Our study which was presented in the preceding section (Figures 3 and 4) is in good agreement with his conclusion, especially in connection with the conception that NPN and urea N fail to be sensitive indicators of renal disturbance. This fact will unfavorably affect

CHOLELITHIASIS

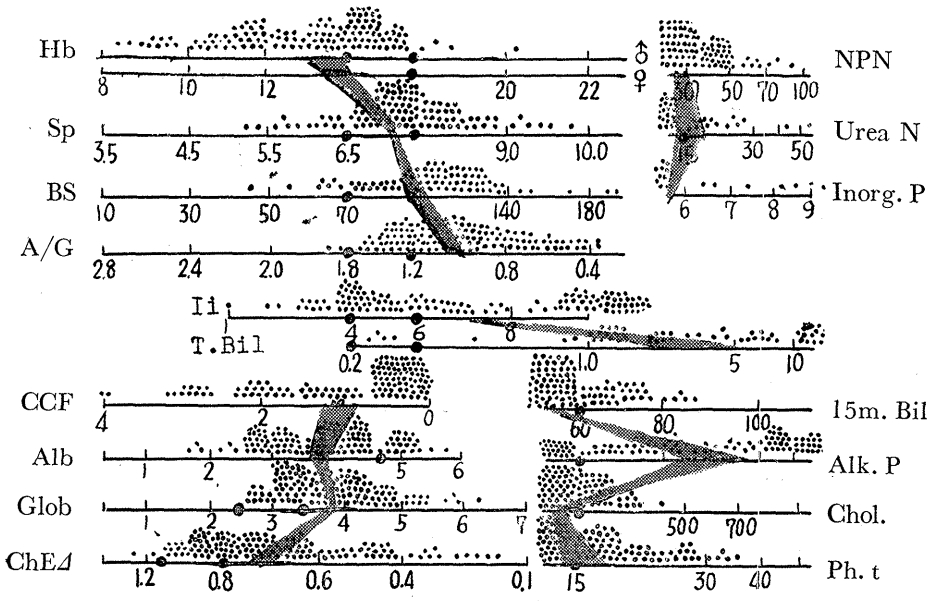


Fig. 37. Blood spectrum of cholelithiasis.

MALIGNANT BILIARY OBSTRUCTION

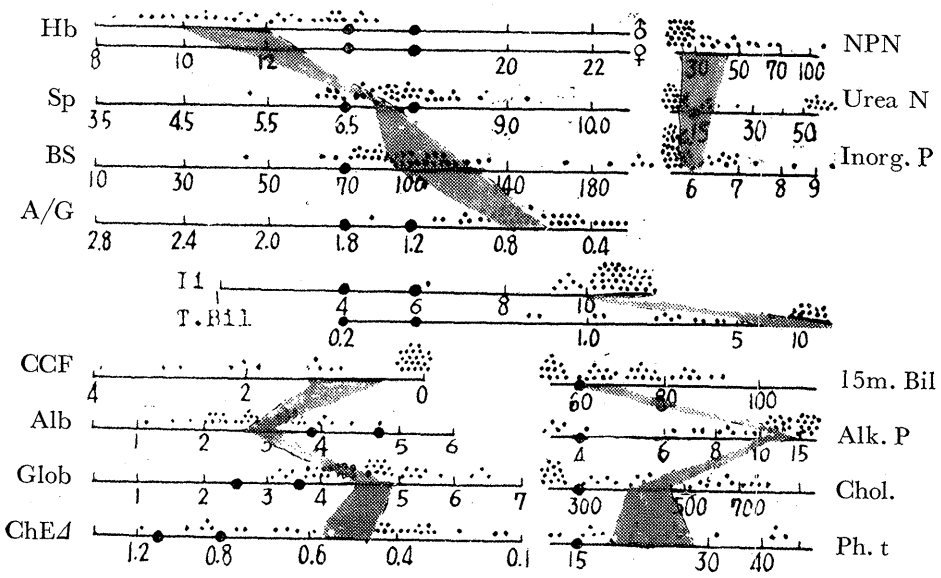


Fig. 38. Blood spectrum of malignant biliary obstruction.

the reliability of the graph of kidney function, since it consists of NPN, urea N and P. Nevertheless, the blood spectrum is obviously helpful for the diagnosis of renal diseases. Nephrotic syndrome and uremia are so distinctly characterized by their specific patterns of blood spectrum that they are diagnosed successfully by the examination of blood chemistry alone. In addition to these disesases, diabetes mellitus showed a specific blood spectrum; the existence of hyperglycemia without appreciable abnormality in other respects is charateristic of the blood spectrum.

The blood spectrum displays its best performance when it is applied to jaundice, which is classified by the method as listed in Table II.

TABLE II

Diagnosis of jaundice by blood spectrum

1. General condition is N or L, while bilary obstruction is N
   ..... Infectious hepatitis.
2. General condition is Z.
   a. Biliary obstruction is 0 (jaundice is very intense; serum bilirubin lies around the level of 15 mg/dl), and hepatic parenchyma is D
      ..... Biliary cirrhosis.
      Malignant biliary obstruction.
   b. Biliary obstruction is .N, and serum alkaline phosphatase is increased to about 10 units.
      α. Hepatic parenchyma (its graph) is slightly distorted, even if it bears pattern ,d
         ..... Benign biliary obstructon.
      β. Hepatic parenchyma (its graph) is distinctly distorted (D)
         ..... Liver cancer.
         Liver abscess.
   c. Biliary obstruction is N, serum alkaline phosphatase is not or very slightly increased, if at all
      α. Severe jaundice (serum bilirubin is around 10 mg/dl)
         ..... Acute and subacute yellow atrophy of the liver.
      β. Slight jaundice··· Live cirrhosis.
         Banti's syndrome.

"General condition," "Hepatic damage" and "Biliary obstruction" refer to the graphs of the relevant items. Notations N, L, ,d, D and 0 indicates the patterns of the the graphs involved in the blood spectrum.

Okabe[9] concluded on the bases of his observation of blood spectrum on the patients with pulmonary tuberculosis that the graph of general condition varied in pattern in the order of N, L, Z and F with enlarging pulmonary lesion. Our study, as described above, corroborates his view, although we could not collect a sufficient number of severe cases. The graph of general condition usually undergoes significant distortion when the tuberculous lesion has advanced to the extent of affecting the total area of unilateral pulmonaryfield as examined

radiologically. A similar tendency is also observed with the graph of hepatic function. Abnormality in blood spectrum is remarkable in exudative pleurisy rather than in pulmonary tuberculosis. Lobor pneumonia and pulmonary cancer showed distinctly distorted pattern of blood spectrum.

Leukemia constitutes a unique entity among the blood diseases owing to its relatively conspicuous distortion in the graph of hepatic parenchyma associated with the appreciable increase in alkaline phosphatase activity.

The differential diagnosis of gastroduodenal cancer and gastric cancer by blood spectrum is possible to a certain extent because apart from the presence of anemia, the former disease is frequently free of the impairment in general condition and hepatic function, which is fairly common in the latter.

It will be apparent from the afore-going account that the blood spectrum serves the diagnosis of various kind of diseases, although due allowance should of course be made for the variation of its usefulness depending on the difference in their pathological character. Our experience with 2840 cases, comprising medical as well as surgical patients, is summarized in Table III. This table

TABLE III

Application of blood spectrum

1. Clinically supposed diagnosis was confirmed	213 cases	
Hepatobiliary diseases	(110)	(7.5%)
Hematopoietic diseases	(44)	
Renal diseases	(40)	
Endocrine diseases	(10)	
Others	(9)	
2. Strong clue of diagnosis was obtained	207 cases	
Hepatobiliary diseases	(113)	(7.3%)
Renal diseases	(36)	
Endocrine diseases	(32)	
Hematopoietic dseases	(19)	
Others	(7)	
3. Complication was revealed	590 cases	
Hepatobiliary disturbance	(433)	(20.8%)
Renal disturbance	(51)	
Dehydration	(45)	
Anemia	(29)	
Hyperglycemia	(21)	
Malnutrition	(11)	

Blood spectrum was useful in 35.5% of 2840 cases.

revealed that the blood spectrum was useful for (1) the confirmation of bed-side diagnosis in 7.5 per cent, and (2) contributed to the establishment of clinical

diagnosis which had been entirely enigmatic at the bed side on account of the failure to get clue to diagnosis in 7.3 per cent, and (3) it was helpful for the detection of complications which were covered by the principal diseases (hepatic disturbances, renal disturbances, dehydration, malnutrition etc.) in 20.8 per cent. The blood spectrum served therefore as a useful tool for detection of positive findings of diseases in about 35.5 per cent of cases which came under our examination, and in a few instances it was indirectly helpful even for the diagnosis of the remaining 64.5 per cent, inasmuch as the blood spectrum facilitated the institution of correct diagnosis by affording the negative findings against a particular suspected disease.

However, a diagnostic measure can not be equally efficient in all kinds of diseases. It is usual that a measure which is so useful that it is mandatory for the diagnosis of one disease is little helpful for that of the next. Blood spectrum is not an exception. It is almost useless for the diseases of the nervous system and of the skin, whereas it is effective well for diagnosis of hepatic, renal and endocrine diseases because the neurologic and dermotologic maladies hardly entail an appreciable alteration in blood chemistry on which the blood spectrum is established. This is the limitation of the application of blood spectrum.

Summary and Conclusion

A complete blood spectrum which consists of the graphs of general condition, hepatic parenchyma, biliary outflow and kidney function was applied to 2840 cases of patients in order to evaluate its usefulness for the diagnosis of various kinds of diseases. By this study the blood spectrum was confirmed to be a well-established system of clinical diagnosis based on blood chemistry, which provided the measures effective in appraising the functions of important organs (liver, kidney etc.) as well as of the general condition. In not a few cases the determination of the name of diseases by blood spectrum was possible without special reference to the records of physical examination, so long as the morbid history was available.

(1) Nephrotic syndrome, uremia and diabetes mellitus showed the peculiar blood spectrums, which enabled us to make their diagnosis without the aid of the record of morbid history and physical examination.

(2) The blood spectrum was very useful for the diagnosis of jaundice and renal diseases. It was also helpful for the observation of the clinical course of pulmonary tuberculosis and anemia, and fairly contributory to the differential diagnosis of gastric cancer and gastroduodenal ulcer.

(3) Blood spectrum served the confirmation of bed-side diagnosis in 7.5 per cent, the establishment of clinical diagnosis which had been entirely enigmatic at the bed side in 7.3 per cent, and the detection of complications (azotemia,

dehydration, malnutrition etc.) in 20.8 per cent of the cases which came under our observation.

The blood spectrum is accordingly believed to be an excellent system of clinical chemistry as judged from the present status of the development of this medical science.

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