SOME NOTES ON THE LIVER FUNCTION AND ALTERED BIOCHEMICAL ASPECTS IN BACILLARY DYSENTERY

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In connection with pro and con discussions on identity of *Ekiri* with bacillary dysentery, innumerable investigations[1-3] chiefly on the hepatic functions have been made in the field of pediatrics, resulting in general recognition of their definite impairment in *Ekiri*. Concerning the similar problems in bacillary dysentery in adults, however, few reports are available in the recent literature.

For this reason we have conducted series of clinical and biochemical studies on problems centered around hepatic functions in adult cases of bacillary dysentery admitted to our clinic.

MATERIALS AND METHODS

Ninety adult patients with bacillary dysentery who were hospitalized in our clinic in a recent year were studied. These patients were classified as follows: 46 cases of B. Flexner II, 20 cases of B. Flexner III, 24 cases of negative bacteriological finding. The bacteriologically negative patients presented all the characteristic symptoms and signs of bacillary dysentery such as fever, tenesmus, and mucous or mucopurulent stool, though no growth was obtained on S. S. agar plate at admission. They were classified as mild cases of dysentery for convenience. As a rule, medication was given according to the following precautions: either sulfaisoxazole in doses of 6.0 gm daily or chloramphenicol in doses of 1.5 gm. daily for 3 days. After a certain interval between medication, these

two drugs were administered alternately until the patients became bacteriologically negative.

Physicochemical studies of blood in this series covered quantitative estimations of the following constituents; serum protein concentration, serum A/G ratio, serum albumin and globulin concentration, blood sugar, serum icteric index, hematocrit, hemoglobin, serum cholinesterase activity (Takahashi-Shibata's method[4]), serum NPN, cephalin-cholesterol flocculation test, thymol turbidity test (Kunkel's method), serum total cholesterol, serum inorganic phosphorus. Blood guanidine was determined within two days of admission by Andes-Meyer's method[6] slightly modified by Okuda and Uchida[5] of our clinic.

Detoxicating function of the liver was studied by santonin test (urinary test for estimating the capacity of converting santonin soda into an unknown oxidized product which gives red color when alkali is added to the urine) and by protein-loading urobilinogen test[7].

Excretory function of the liver was examined by means of bromsulfalein retention test (BSP test). Retention at 30 minutes after injection was recorded.

Repeated examinations were not, in general, available on account of the short course of the illness.

Results and Discussion

(1) *Hemoglobin value* (Fig. 1)

The hemoglobin value was slightly or moderately decreased in 17.0 % of 47 males and 41.4 % of 29 females. There was little indication of correlation between the change in hemoglobin concentration and the severity of symptoms or presence or absence of bacilli, although the hemoglobin decrease tended to become gradually more pronounced with the lapse of time in three protracted cases.

(2) *Hematocrit value* (Fig. 2)

A slight decrease in hematocrit was observed in 8.2 % of 49 males and 46.4 % of 28 females. Females appeared to be more susceptible to the hematocrit fall than the males. Marked decrease was encountered in the later stage of protracted cases, despite the fact that it was not directly related to the intensity of symptoms, and to the frequency of stools in particular. Our data therefore do not confirm the findings of Nishiyama[8] who reported a rise in hematocrit in bacillary dysentery.

(3) *Serum protein concentration* (Fig. 3)

The level of serum protein was lowered slightly in 16.7 % of 84

Fig. 1

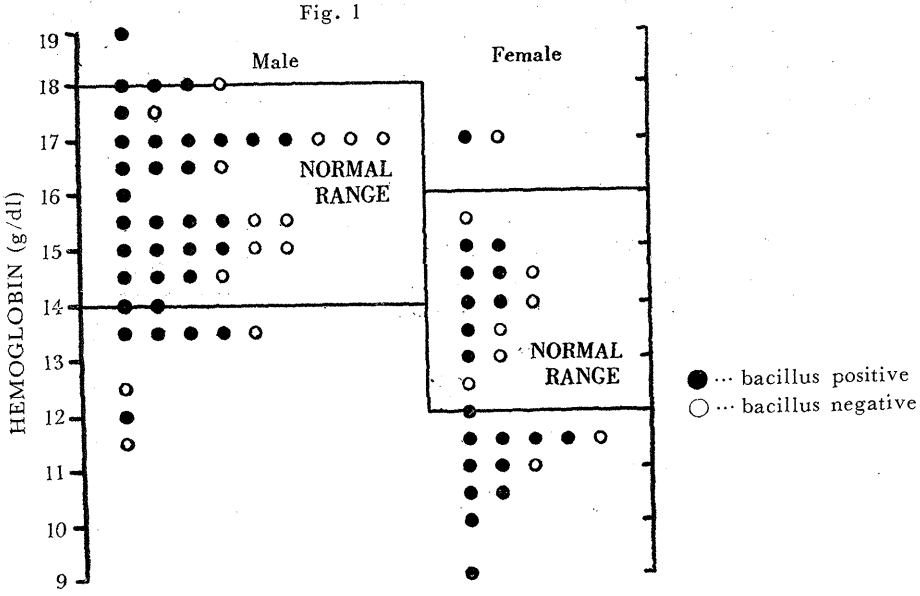


Fig. 2

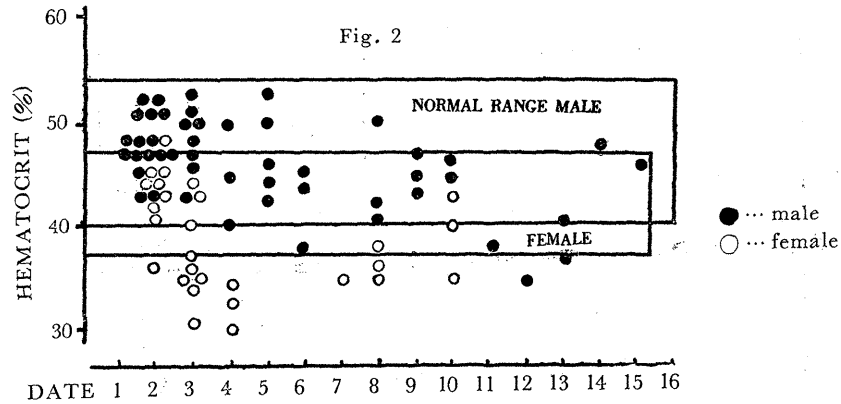
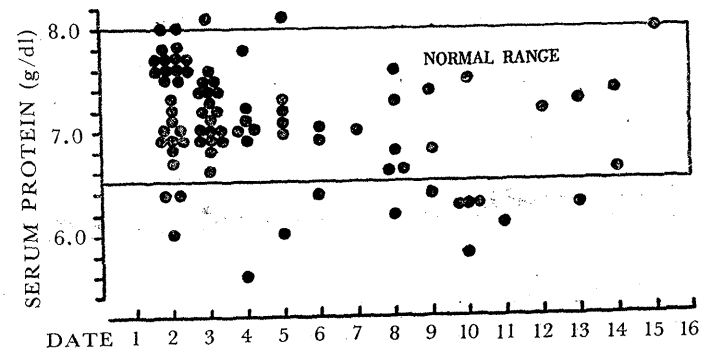


Fig. 3



patients and had tendency to fall more remarkably with the length of the clinical course. Nishiyama[8] and Abe[9] have reported that the absolute serum protein volume was decreased in the early stage of dysentery, although its concentration was maintained within the normal range because of the reduction in the volume of circulating plasma.

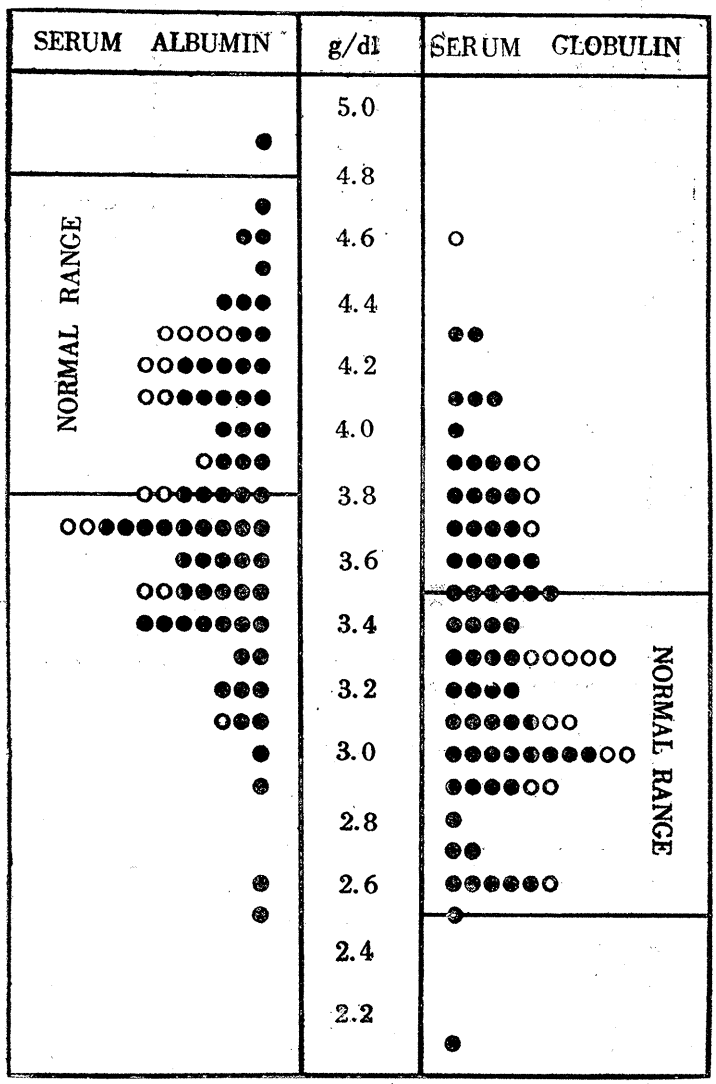


Fig. 4

● ····· bacillus positive
○ ····· bacillus negative

(4) *Serum albumin and globulin concentration* (Fig. 4)

Concentration of serum albumin was reduced in 50.7 % of 73 cases of patients with positive culture of bacilli, and in 31.1 % of 16 cases of bacillus-negative cases, while its diminution was found in 50.0 % of entire patients. The serum globulin concentration was slightly elevated in 25.0 % of 73 bacillus-positive patients, in 31.5 % of 16 bacillus-negative cases, and in 32.1 % of the entire cases. In the three protracted cases the reduction of serum albumin was roughly proportionate to the length of the clinical course, whereas there was no alteration in the serum globulin concentration.

(5) *The ratio between serum albumin and globulin* (Fig. 5)

The A/G ratio was lowered in 58.5 % of the bacillus-positive and 50 % of bacillus-negative groups, i.e., in 57.1 % of the entire patients.

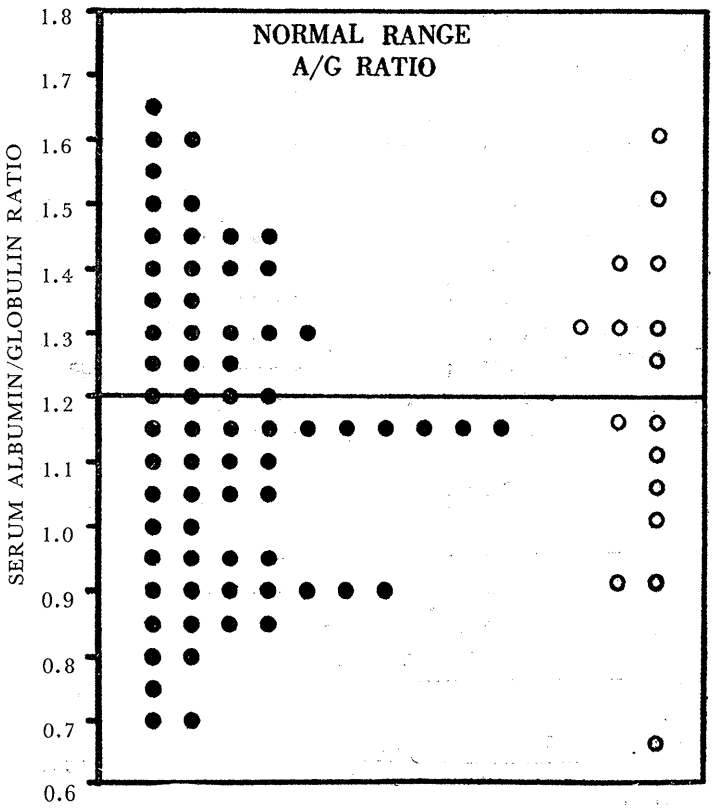


Fig. 5

● ····· bacillus positive
○ ····· bacillus negative

Although in the protracted cases in which the ratio was studied later than tenth day of illness it was more often reduced than not, yet this reduction in the ratio has taken place, as in ten cases of decrease in the serum albumin and globulin concentration, in the earlier stages of the disease, and cannot be considered as possessing a definite relationship with the duration of the disease. In 44 cases in which A/G ratio was determined in the third day of admission, it was found already reduced in 59.1 %.

(6) *Blood sugar* (Fig. 6)

Blood sugar level was normal in 53.2 %, elevated in 18.8 %, and lowered in 28 % respectively, of the 75 patients. Estimation made before the third day of hospitalization showed a normal value in 50 %, increase in 11.9 % and decrease in 35.1 %, the percentage of the patients with lowered blood sugar level being prominent. Nine days after admission and thereafter, however, there was no instance that showed a decrease in the blood sugar concentration.

Abe and his coworkers[10] have pointed out that the blood sugar level tended to fall on the third day of illness and ascribed it to the effect of fasting. The date we have presented above would seem to support their view, especially since in our study the hypoglycemia was no longer encountered in the later stages when the patient was able to take sufficient food. Whereas Kawaguchi et al[2] have recognized the impairment in the ability to utilize glucose in the early stage of *Ekiri*, we consider the rise in the blood sugar in our study to be the result of either a hepatic functional impairment or decrease in the function of sugar utilization.

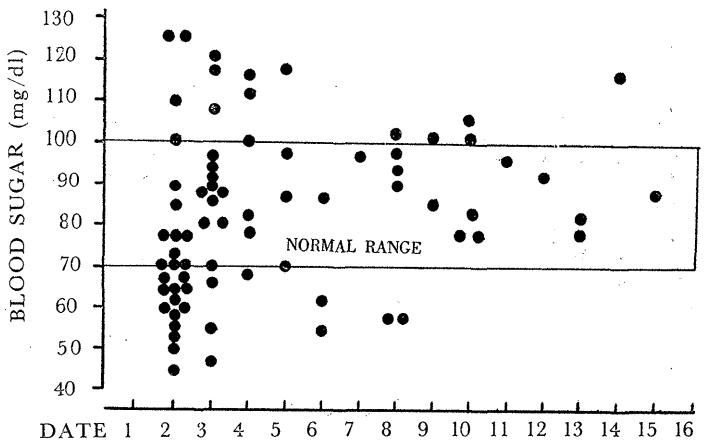


Fig. 6

(7) *Cephalin-cholesterol flocculation test* (Fig. 7)

This test was positive in 39.8 % of 88 patients, suggesting the presence of hepatic damage. There was no special correlation between the results of this test and the course of illness.

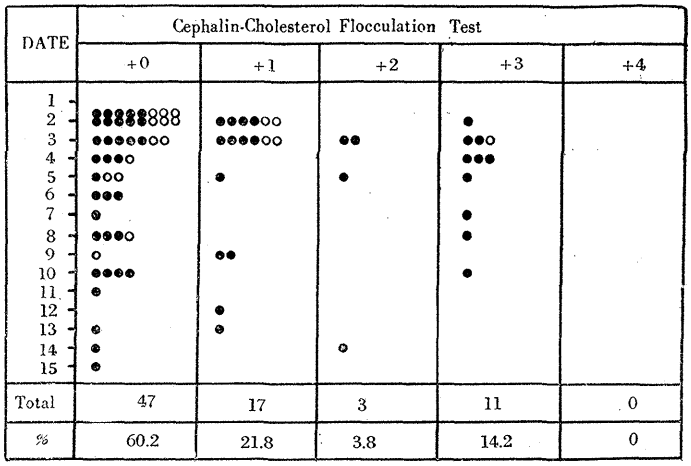


Fig. 7

● ····· bacillus positive
○ ····· bacillus negative

(8) *Serum icteric index*

A slight rise in the serum icteric index was noted in four out of 78 patients, and even in these cases an increase of the total serum bilirubin did not accompany the rise in icteric index. Murata[11] has demonstrated an elevated serum bilirubin level in the early stages of dysentery, which returns toward normal with impairment of the patients conditions. We have demonstrated intracellular bilirubin granules in the liver cells by biopsy in spite of the fact that there was no recognizable rise in the serum icteric index. This fact suggests a possiblility of occurrence of bilirubinemia in some cases of dysentery.

(9) *Serum nonprotein* (NPN)

Although it was reported by Miyakawa[1] that blood NPN is moderately increased in the early stage of dysentery, our findings show that only a slight increase has occurred (34–41 mg/dl as compared to 30 mg/dl of the normal average) in 5 out of 78 cases.

(10) *Serum alkaline-phosphatase, serum total cholesterol, phenol turbidity test, serum inorganic phosphorus*

In hepatic diseases the elevation of these chemical constitutents of blood is regarded as signs of biliary obstruction. In dysentery no marked alteration was noted.

(11) *Serum cholinesterase activity* (Fig. 8)

The serum cholinesterase activity was lowered in 72.1 % of 61 cases of bacillus-positive and in 42.1 % of 19 cases of bacillus-negative patients. The degree of the lowering was more marked in the former, one of them showing the decrease of as low as ΔpH 0.3 as compared to the normal ΔpH 0.8–1.1. The great majority of protracted cases exhibited a tendency to subnormal activity of serum cholinesterase in the latter stage. Such subnormal value was invariably noticed in the cases with mucous or mucosanguinopurulent stool, but it had no relation to fever, frequency of diarrhea and the degree of tenesmus.

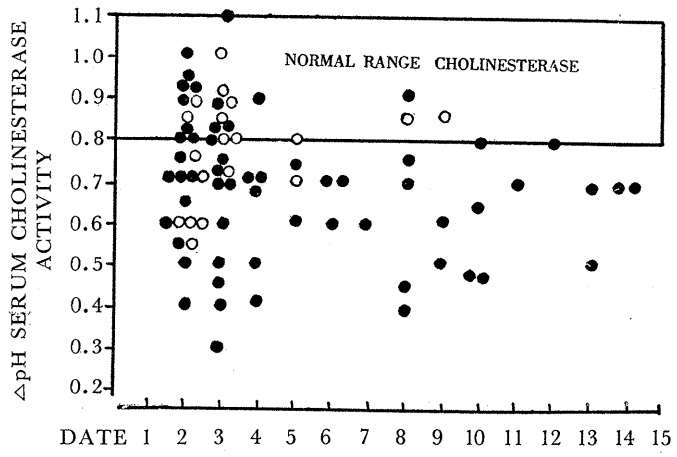


Fig. 8

● ····· bacillus positive ○ ····· bacillus negative

According to Vorhaus and Kark [12] who have contributed detailed report on this problem, the serum cholinesterase is lowered in diseases of the liver, malnutrition, acute infectious diseases and anemia and this reduction is related to a damage of hepatic parenchyma and to decrease of serum albumin. Farber [13] also confirmed the correlation between the serum cholinesterase and serum albumin. In our cases, however, the serum cholinesterase activity was lowered in all those patients whose serum albumin concentration has dropped below 3.4 gm/dl, whereas those in which the serum albumin concentration remained above 3.4 gm/dl showed varible figures for the activity.

Sasaki and Tsuchiya[14] demonstrated a marked decrease of the serum cholinesterase activity in *Ekiri* while it remaines normal in dysentery, and considered this decrease as possibly signifying the occurrence of functional impairment of the liver in *Ekiri*. We agree until this interpretation, although in our study more than half of dysentery cases showing cholinesterase decrease have presented a drop in serum protein group, C.C.F.T., blood sugar, santonin test, and protein-loading urobilinogen test. However, there were quite a number of cases with decrease in cholinesterase and yet showed no accompanying changes in the above mentioned tests except reduction of the serum cholinesterase activity. (See Fig. 9).

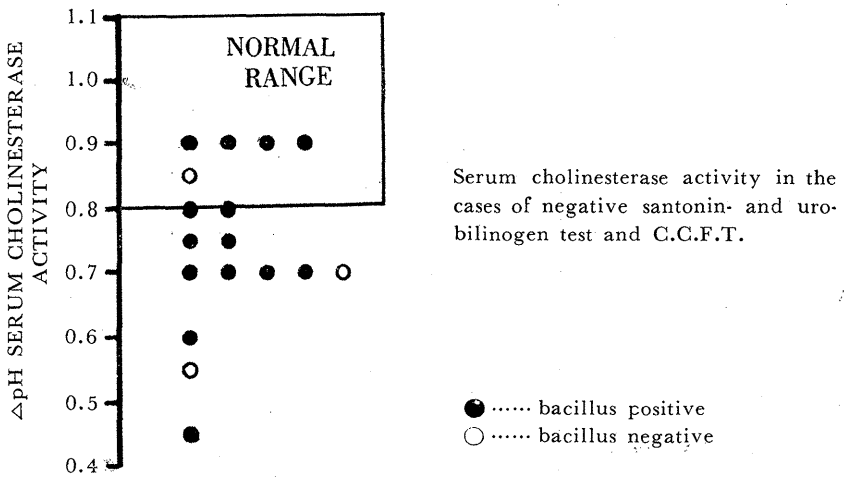


Fig. 9

Liver biopsy was done on two patients with lowered serum cholinesterase, and the results are as listed on Table I. The specimen numbered I showed no damage to the hepatic parenchyma except for a slight deposit of intracellular bilirubin granules, although an impairment of detoxicating function of the liver, and although clinical and laboratory findings have proved the existence of lowered activity of serum cholinesterase (ΔpH 0.4), impaired detoxicating function of the liver, and the lowered serum albumin level as well as increased guanidine concentration. The specimen numbered II was histologically quite normal notwithstanding the lowered cholinesterase activity (ΔpH 0.5), the possitive santonin detoxication test and the high blood guanidine level. From these findings we have learned that the serum cholinesterase activity may drop markedly even though the histological picture of the hepatic parenchyma

shows no abnormality with haematoxylin-eosin technique.

We encounter many cases of such gastrointestinal diseases as do not as a rule induce definite hepatic damage and yet present lowered serum cholinesterase activity. In view of the several data detailed in the preceding pages, it would seem impossible to attribute the reduction of the serum cholinesterase activity in dysentery to a hepatic damage alone, but some extrahepatic factors must also be considered as causative agent such as disturbance in the gastrointestinal tract. In fact, we were able to demonstrate reduction of the cholinesterase activity of the serum, slight though it was, by adding dysentery bacillus proper or its broth culture, and are inclined to presume that there are in the digestive tract some potent inhibitory factors for the serum cholinesterase activity.

TABLE I

Specimen	I (♂)	II (♂)	Normal range
Date	5th day	2nd day	
Hemoglobin	14.5	14.6	14–18 g/dl
Hematocrit	43.5	44.5	40–54 %
Serum protein	6.0	6.9	6.5–8.0 g/dl
Serum albumin	3.3	3.9	3.8–4.8 g/dl
A/G ratio	1.25	1.27	1.2–1.8
Blood sugar	70	54	70–100 mg/dl
Icteric index	5	5	4–6
Cholinesterase	0.4	0.5	0.8–1.1 ⊿PH
C.C.F.T.	0	0	0
N.P.N.	27	23	20–30 mg/dl
Cholesterol	300		160–300 mg/dl
Alk. phosphatase	0.7	2.7	1–4 u.
Inorganic phosphor	4.1	3.7	2–5 mg/dl
Phenol turbidity	9.9	7.3	8–15 u.
Guanidine	0.22	0.26	Below 0.1 mg/dl
Santonin test	+	+	−
Urobilinogen test	+	−	−
Liver biopsy	Intracellular bilirubin pigmentation	Normal	

(12) *Santonin detoxicating test* (Fig. 10)

The santonin detoxicating test was negative in 62.5 %, doubtful in 25.0 %, and positive in 12.5 % of 9 cases of bacillus-negative patients.

Among the bacillus-positive cases, on the other hand, the test was positive in 35.9 % of 38 cases. The test thus shows a rather marked impairment of ability of santonin disposal as compared to the bacillus-negative group. There was little correlation between the test and severity of the symptoms to be noted.

Murakami [15] injected dysentery toxin in the rabbit, and demonstrated the resulting impairment of santonin detoxicating ability of the rabbit's serum, apparently casting some light upon the interpretation of our observation.

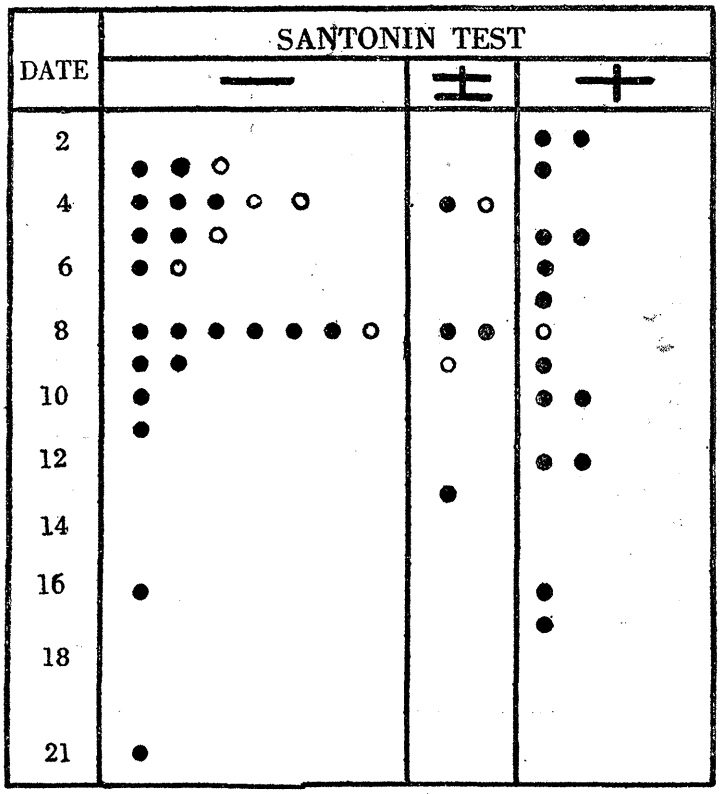


Fig. 10

● ····· bacillus positive ○ ····· bacillus negative

(13) *Protein-loading urobilinogen test* (Fig. 11)

This test which is employed in estimating the urinary urobilinogen after loading with milk and egg can also be applied in determination of the index of detoxicating capacity of the liver [7]. The test made on

dysentery patients gave 66.7% negative, 33.3% positive for bacillus-negative cases and 40.9 % negative and 59.1 % positive for the bacillus-positive cases; thus definitely higher rate of hepatic impairment in the bacillus-positive dysentery is demonstrated.

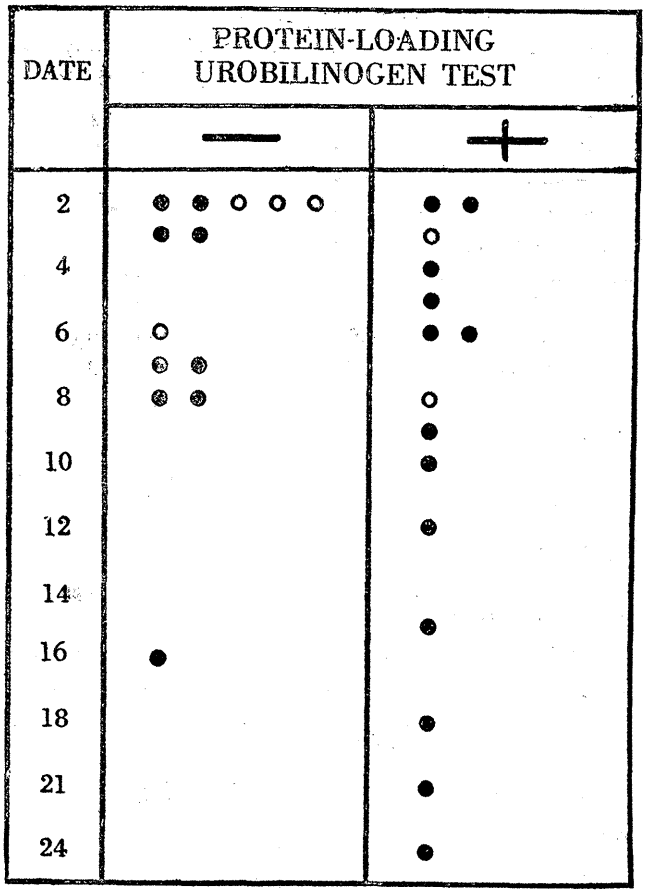


Fig. 11

● ····· bacillus positive ○ ····· bacillus negative

The results of this test are, as shown in Table II, quite in agreement with those of the santonin test, all being concerned with the detoxicating function of the liver.

(14) *Bromsulfalein retention test* (Fig. 12)

This was carried out on 19 patients and was normal in all except one, showing no instance of impaired excretory function of the liver.

Comparing the above results with those of santonin and urobilinogen tests we may state that the hepatic excretory function remains intact while the detoxicating function definitely reduced in bacillary dysentery, there being thus dissociation of functions into excretory and detoxicating.

TABLE II

The Relation between Santonin Test and Urobilinogen Test

S-Test	U-Test	Cases
+	+	8
−	−	7
±	+	2
±	−	1
+	−	0
−	+	1

(15) *Blood guanidine* (Fig. 13)

The blood guanidine estimated on the second or third day after admission was slightly increased in all of 7 cases of bacillus-negative patients and markedly increased in all of 14 cases of bacillus-positive cases.

Igarashi[16] and Imamura and Hirai[17] similarly demonstrated an elevation of blood guanidine level in early stages of dysentery and *Ekiri*.

(16) *The difference due to the variation of bacillary type.*

All of the various tests and analyses that are described in the previous pages were repeated on patients divided into group one with Flexner type II and the other with Flexner type III bacilli. No difference whatever was found in the results.

(17) *The influences of drugs upon the liver functions.*

One of us[18] had reported elsewhere that sulfaisoxazol has a stimulant effect upon the liver function, but in the present series of study we found no deleterious effect of either chloramphenicol or sulfaisoxasole upon hepatic functions.

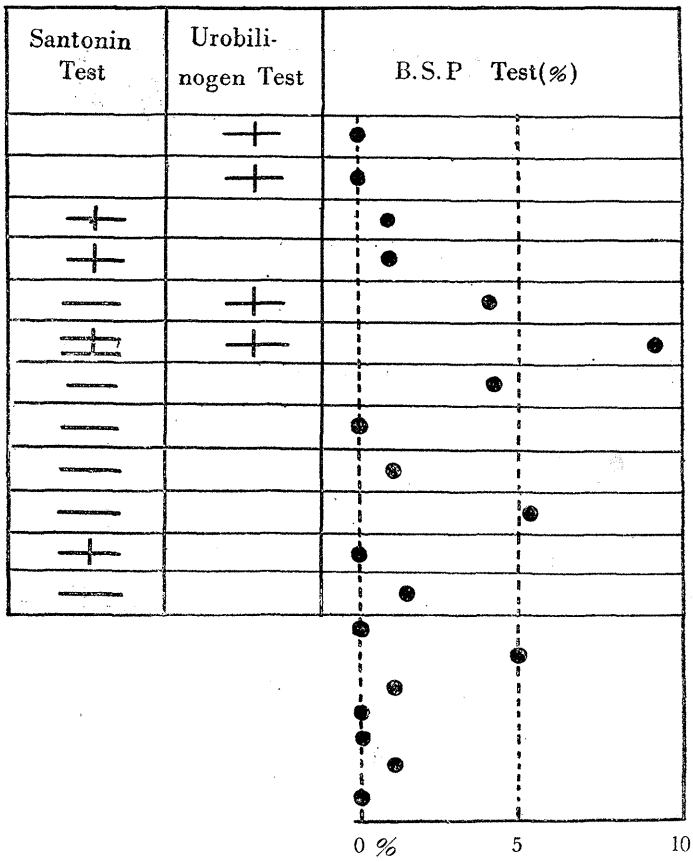


Fig. 12

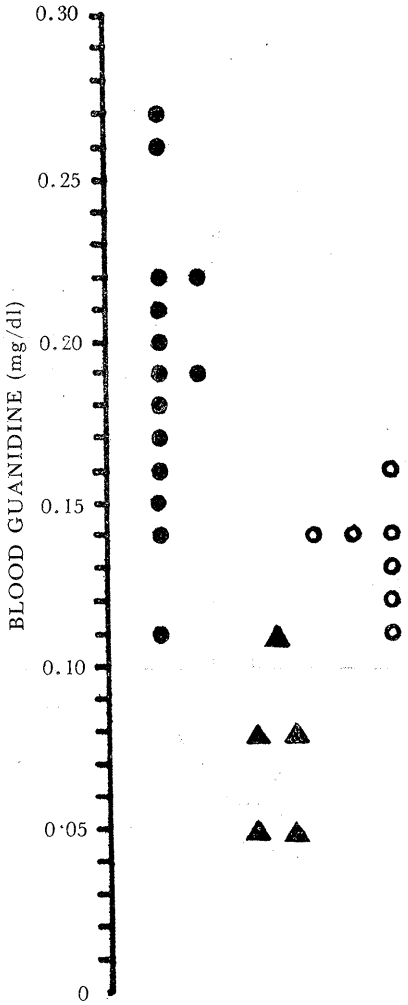


Fig. 13

● ····· bacillus positive
○ ····· bacillus negative
▲ ····· normal adult

Summary and Conclusions

The results of our various clinical laboratory investigations centering around hepatic functoins in bacillary dysentery in adult may be summarized as follows:

1. Hemoglobin level was lowered in 41.4 % and hematocrit in 46.4 % from slightly to moderately of all the women patients, whereas of the man patients only 17.6 % showed lowered hemoglobin and 8.2 % reduced hematocrit level.

2. The serum protein concentration was slighly decreased in 16.7 % of 84 patients, and the decrease became increasingly pronounced with the prolongation of clinical course. Serum albumin was decreased in 50.0 %, but globulin was increased in 32.1 % of 89 patients. The albumin/globulin ratio was reversed in 57.1 % of cases.

3. The blood sugar level under fasting conditions was either elevated or lowered in the early stage, but this was not found in the later stage.

4. The cephalin-cholesterol flocculation test was positive in 39.8 % of 88 patients.

5. The serum icteric index was raised in only 5.1 % of 78 patients.

6. The serum non-protein nitrogen was increased in only 6.4 % of 78 patients.

7. Serum alkaline phosphatase, serum total cholesterol, phenol turbidity test and serum inorganic phoshorus remained within normal limits in all the patients examined.

8. The serum cholinesterase activity was lowered in 72.1 % of 61 cases of bacillus-positive and in 42.1 % of 19 cases of the bacillus-negative patients, and the degree of its lowering was more marked in the former. This lowing of activity is considered to be due not only to the hepatic but to some extrahepatic factors as well. The liver biopsy study of the two patients in whom the serum cholinesterase activity was markedly reduced showed no noticeable histological changes.

9. The santonin test and the protein-loading urobiliongen test revealed impaiment of detoxicating function of the liver in about a half of the cases.

10. The BSP retention test was carried out in 19 patients and was found normal except in one, suggesting the existence of dissociation between the excreting and detoxications of the liver in dysentery.

11. The blood guanidine was markedly elevated in the early stage of the bacillus-positive group, while it was only slightly elevated in the bacillus-negative group.

ACKNOWLEDGEMENT

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