STUDIES ON SERUM CHOLINESTERASE*

II. SERUM CHOLINESTERASE IN DISEASES

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(Received February 2, 1956)

Study of cholinesterase activity in vaious tissues has revealed that cholinesterase is not a single enzyme. One classification groups the cholinesterases into two broad classes, the "true" cholinesterases and the "pseudo" cholinesterases. The two classes of cholinesterases are distinguishable from each other in terms of substrate specificity. Thus, though both "true" and "pseudo" cholinesterase will act upon acetylcholin, other choline esters (propionylcholine, benzoylcholine) are much less readily hydrolyzed by the "true" cholinesterase than is acetylcholine; whereas the revers is true for the "pseudo" cholinesterase, which will, for example, rapidly decompose benzoylcholine. The cholinesterase of blood serum belong to the class of "pseudo" cholinesterase[1], and it is one of the serum protains whose precise physiological function is not yet clear[2-4]. Interest in serum cholinesterase has been heightened by the discovery that the enzyme undergoes a considerable reduction in activity in hepatic disorders, particularly in liver cirrhosis, althongh various degrees of the diminishd activity are encountered also in other diseases. Numbers of reports[4-10] have been published since 1937, but their results have been rather diversified in a certain kinds of pathological conditions. Moreover there have been series of pro-and-con-disputes on the evaluation of the determination of serum cholinesterase as an aid to the detection of hepatic dysfunction in the extra-hepatic diseases. A study on serum cholinesterase was therefore undertaken with a good number of patients with multifarious diseases as materials, employing our phenol-red comparator method which has been described in another paper[11] for its estimation, with the intention of reviewing the change in the activity of this enzyme in a variety of diseases. The purpose of this paper is to present the results obtaind in our study.

METHOD

Two thousand and eight hundred samples of blood sera, which were received

* Aided by grant from the Ministry of Education.

by the Department of Clinical Pathology, the Yamaguchi Medical College Hospital, with the object of routine examination of clinical chemistry for the past three years, were subjected to the phenol-red comparator procedure[10] for estimation of serum cholinesterase. The sera were obtaind from the patients with diseases listed in Table 1, including the cases of gyneco-obstetrics, dermatology, ophthalmology, and otolaryngology as well as of internal medicine and surgery. The diseases were classified into eithteen groups according to the difference in the organ systems of the principal pathological lesion, and the groups were compared with each other in the confidence limits ($\alpha=0.05$) of their average values of serum cholinesterase activity. Standard deviations* were also calculated. Rare diseases were omitted, unless they had relevance to our special interest.

Results

The results obtained are depicted schematically in Figures 1 to 4. Table 1

Table I.

A list of the average activy of serum cholinesterase in diseases

⊿pH 0.31–0.49: Lesions and tumors of the spinal cord, Septicemia, Liver cirrhosis, Cysts and tumors of the mediastinum, Myoma, Neoplasms of the liver (primary and secondary).

⊿pH 0.50–0.59: Pemphygus, Gastric cancer, Cancer of the gall bladder and bile ducts, Ileus, Liver abscess, Cancer of the lungs, Cancer of the prostate gland, Malignsnt neoplasms of the ovaries and tubes, Purulent meningitis, Infections mononucleosis, Peritonitis, Rheumatism, Heart failure.

⊿pH 0.60–0.69: Cancer of the rectum, Lymphosarcoma and Hodgkin's disease, Hepato-splenomegaly (Banti's syndrome), Pancreatitis, Cysts and tumors of the pancreas, Diarrhea, Malignant otorhinopharyngeal tumors, Endocarditis, Burns (electrical and other), Anemias, Pleurisy with effusion, Malignant neoplasms of the skin, Infectious hepatitis, Nephrolithiasis, Dysentery, Toxemia of pregnancy and Eclampsia, Cancer of the breast, Gasstric ulcer, Biliary obstruction.

⊿pH 0.70–0.79: Urticaria, Penal tuberculosis, Cysts and tumors of the kldney, Cardiac asthma, Uterine cancer, Advanced pulmonary tuberculosis, purpura, Cerebral hemorrhage, Ovarian cyst, Encephalitis, Addison's disease, Parkinsonism and Epilepsy.

⊿pH 0.80–0.89: Eruptions, Eczema, Dermatitis, Moderately advanced pulmonary tuberculosis, Erythema, Optic tumors, Tuberculosis of the bones and the joints, Gastritis, Sciatica, Diabetes mellitus, Fructure of the bones, General paralysis of the insane, Poliomyelitis, Acute glomerulonephritis, Cerebral tumors, Psychosis, Pyodermia, Sclerodermia, Herpes zoster, (Normal person), Hypothyroidism, Vascular hypertension.

⊿pH 0.90–0.99: Slight pulmonary tuberculosis, Bronchial asthma, Tuberculous meningitis, Hyperthyroidism.

⊿pH 1.09: Nephrosis.

* The width of the confidence limits of average value bears closer relation to the magnitude of the number of samples rather than to the scattering of the distribution of individual estimations of the samples. The range of scattering is indicated by the standard deviation in Gaussian distribution, but only approximately in the skew curve distribution. In many kinds of diseases as well as in normal persons the serum cholinesterase forms non-Gaussian skew distribution (Fig. 5).

summarizes the diseases in the order of lowered activity of serum cholinesterase. A brief remark will be made about the individual groups of diseases.

(1) Infectious diseas. Medium decrease in serum cholinesterase (ΔpH around 0.6) was common in the ordinary cases of infectious diseases, while in tuberculosis, especially of the lungs, the diminution was slight (ΔpH 0.7–0.8) exceptionally pronounced fall (ΔpH 0.4) was encountered in septicemia. There was little distinction in the pattern of the drop of serum cholinesterase activity between the acute and chronic cases.

(2) Allergic diseases. Slightest rise in serum cholinesterase activity was

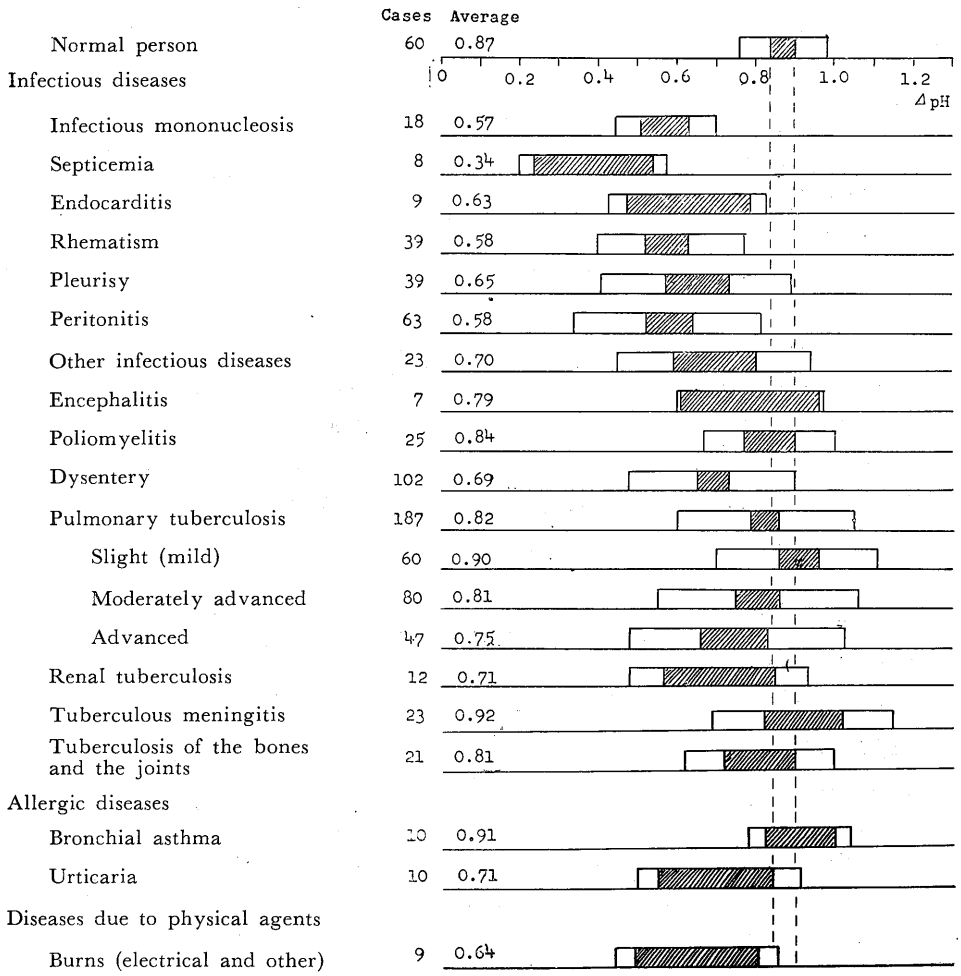

Fig. 1 Serum cholinesterase in diseases (1)
Shaded area represents the confidence limits (α=0.05) of the average, and white area indicates the range of the average ± standard deviation.

encountered in bronchial asthma, while slight fall (⊿pH 0.7) was found in urticaria.

(3) Diseases of the digestive organs. Hepatic diseases entailed a marked

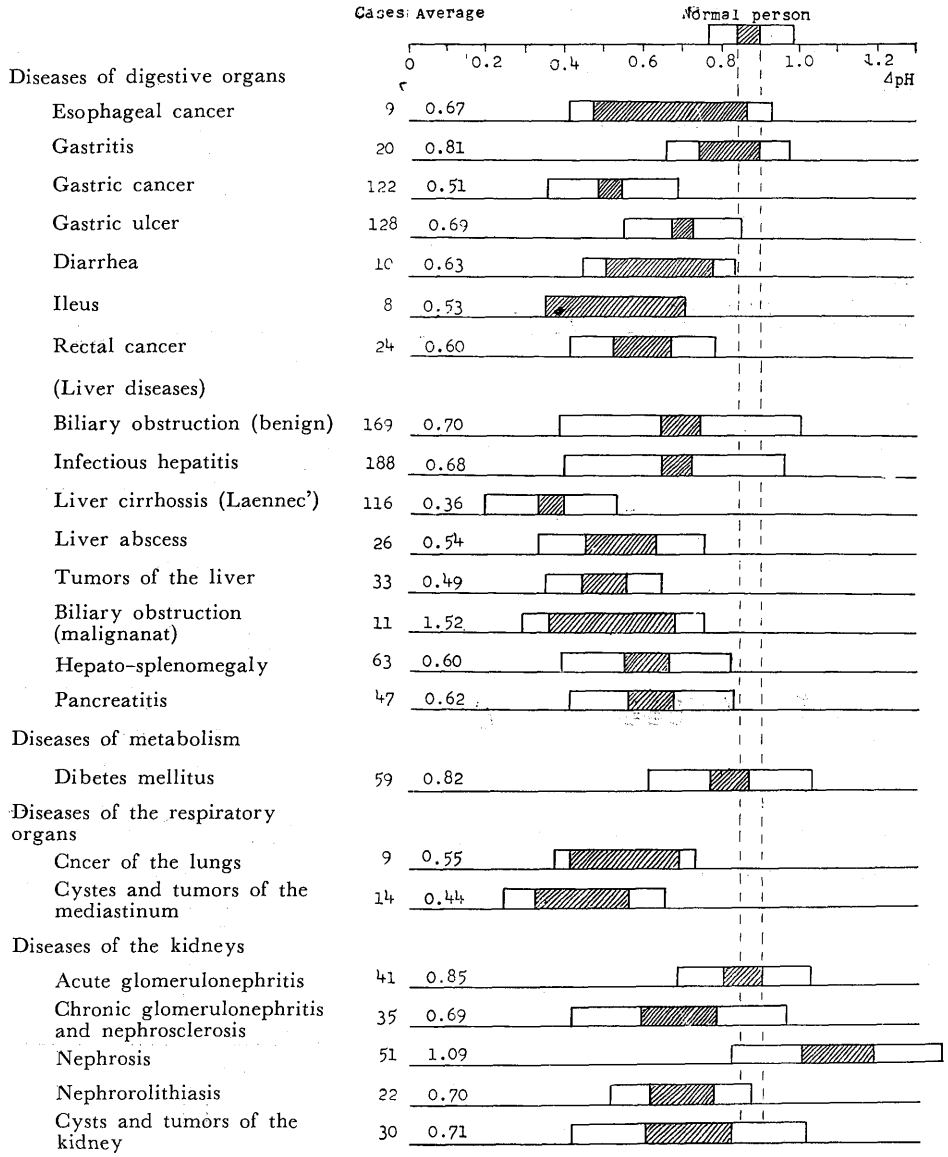

FIG. 2 Serum cholinesterase in diseases (2)

Shaded area represents the confidence limits ($\alpha=0.05$) of the average, and white area indicates the range of the average ± standard deviation.

reduction in serum cholinesterase (ΔpH below 0.6), althorgh low activity (ΔpH around 0.6) was universal in other digestive diseases. The characteristic features of the change in serum cholinesterase in the hepatobiliary diseases are listed in Table 2.

(4) Diseases of metabolism. Serum cholinesterase was either normal or

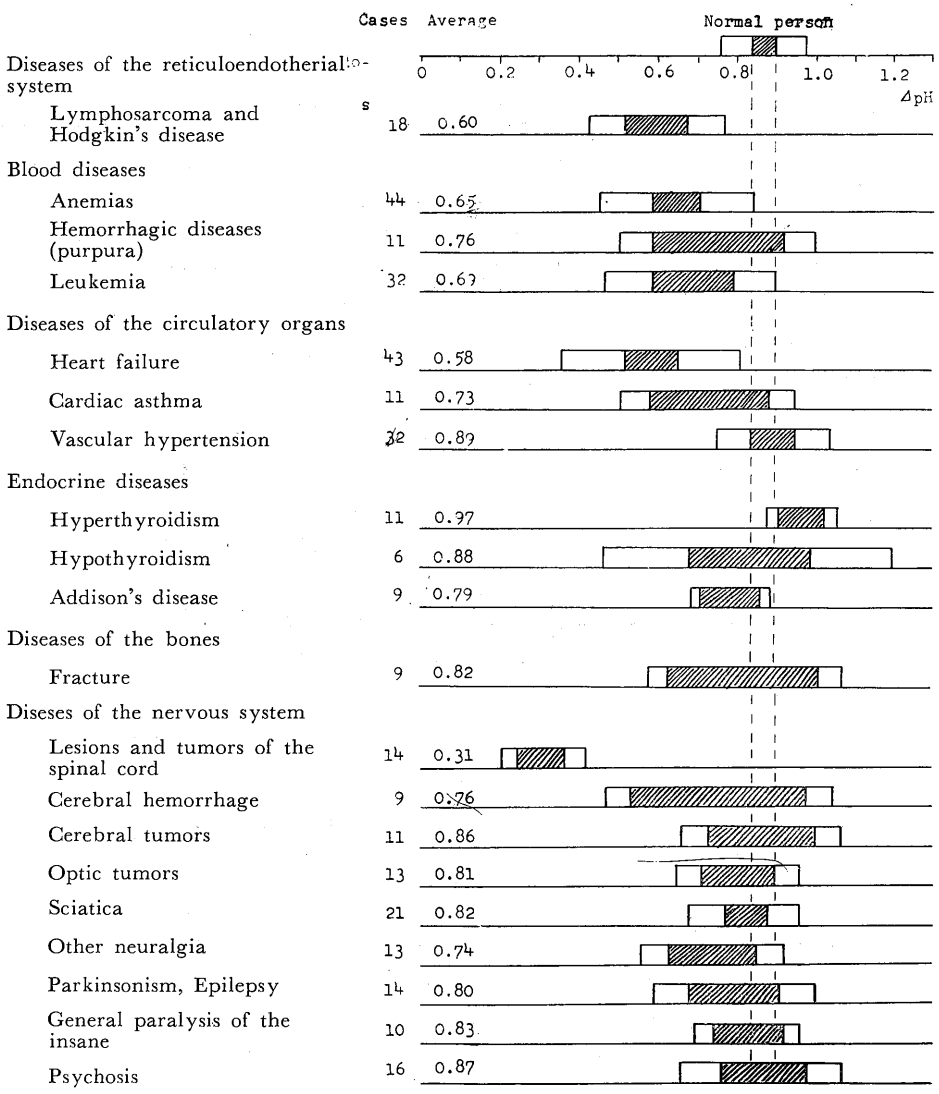

Fig. 3 Serum cholinesterase in diseases (3)

Shaded area represents the confidence limits (α=0.05) of the average, and white ara indicates the range of the average ± standard deviation.

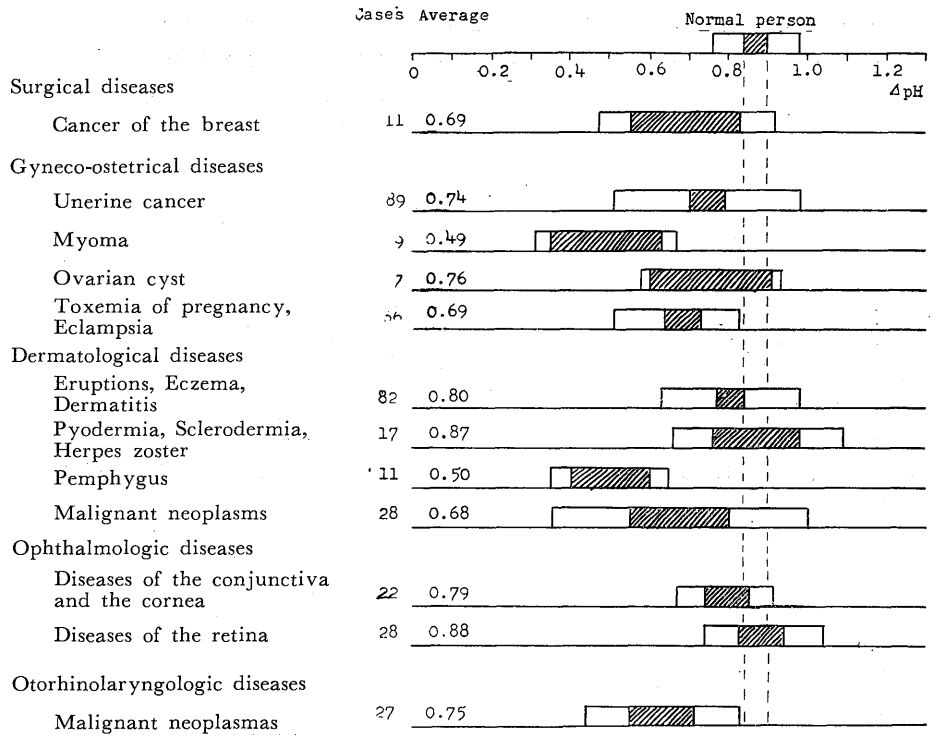

Fig. 4 Serum cholinesterase in diseases (4)
Shaded area represents the confidence limits (α=0.05) of the average, and white area indicates the range of the average ± standard deviation.

TABLE II.

Patterns of the lowered serum cholinesterase activity in the Hepatobiliary diseases

A. Parenchymatous diseases of the liver	
Decrease pronounced in chronic cases (liver cirrhosis)	Decrease slight in acute cases (tumors of the liver)
Decrease pronounced in chronic diffuse lesion of the liver (liver cirrhosis)	Decrease moderate in chronic localized lesion of the liver (tumors of the liver)
B. Jaundice (Menifest and latent)	
Decrease pronounced in parenchymatous jaundice (liver cirrhosis)	Decrease slight or moderate in obtructive jaundice (cholelithiasis)
Decrease moderate in malignant biliary obstruction (cancer of the biliary tract)	Decrease slight in benign biliary obstuction (cholelithiasis)

Decrease prounced : ΔpH below 0.6 (around 0.4)
moderate : ΔpH around 0.6
slight : ΔpH around 0.7

slightly decleased (ΔpH around 0.8).

(5) Diseases of the respiratory organs. Moderate fall (ΔpH around 0.6) was common in mediastinal tumor and pulmonary cancer. In tuberculosis the decrease was less marked (ΔpH 0.7–0.8) as described above.

(6) Renal diseases. Nephrosis (Type 2 Nephrits) was characterized by the conspicuous rise (ΔpH around 1.1), whereas slight fall (ΔpH 0.7) was general in other types of renal diseases which comprised glomerulonephritis (Type 2 Nephritis), nephrolithiasis and kidney tumors.

(7) Diseases of the reticuloendothelial system. Medium decrease (ΔpH 0.6) was found in lymphosarcoma and Hodgkin's disease.

(8) Blood diseases. Drop of serum cholinesterase activity was not profound in blood diseases (ΔpH around 0.7).

(9) Diseases of the circulatory organs. Circulatory failure caused medium decreas (ΔpH 0.6), but hypertension gave either the normal or the slightly elevated activity.

(10) Endocrine diseases. Slight increase was common in hyperthyroidism, while both increase and decrease were demonstrated in hypothyroidism. Thus the tendency of change was diversified this condition. Addison's disease entailed slight fall (ΔpH 0.75).

(11) Neurologic and psychiatric diseases. The change in serum cholinesterase was not remarkable in these diseases, but myelitis and the gross lesions (tumor and trauma) of spinal cord decreased the enzyme activity to an extreme extent (ΔpH 0.3).

(12) Gyneco-obstetrical diseases. Slight fall (ΔpH 0.7) was common except in uterine myoma which caused a remarkable drop (ΔpH 0.5). In pregnancy the serum cholinesterase activity descended slightly (ΔpH 0.7).

(13) Dermatological diseases. Serum cholinesterase was normal in the majority of cases. Malignant neoplasm decreased the activity either slightly (ΔpH 0.7) or moderately (ΔpH 0.6), and in pemphygus a considerable reduction of activity was encountered (ΔpH 0.5).

Discussion

It is the consensus of opinion[9,10,12–16] that decrease in serum chdlinesterase activity is characteristic of hepatic diseases, although it is also encountered in malnutrition (cachexia)[8,17,18], acute infection[7,10,19] and blood diseases[20,21]. The data of our study described above corroborates the view. The terms malnutrition and cachexia are convenient when used to refer to the impaired general conditions which are accompnied by the secondary hepatic dysfunction, although they are not desirable for the exact critic because of its vague definition. The

drop of serum cholinesterase activity in malnutrition is therefore generally understood as one of the results of the disturbance in hepatic function which can not

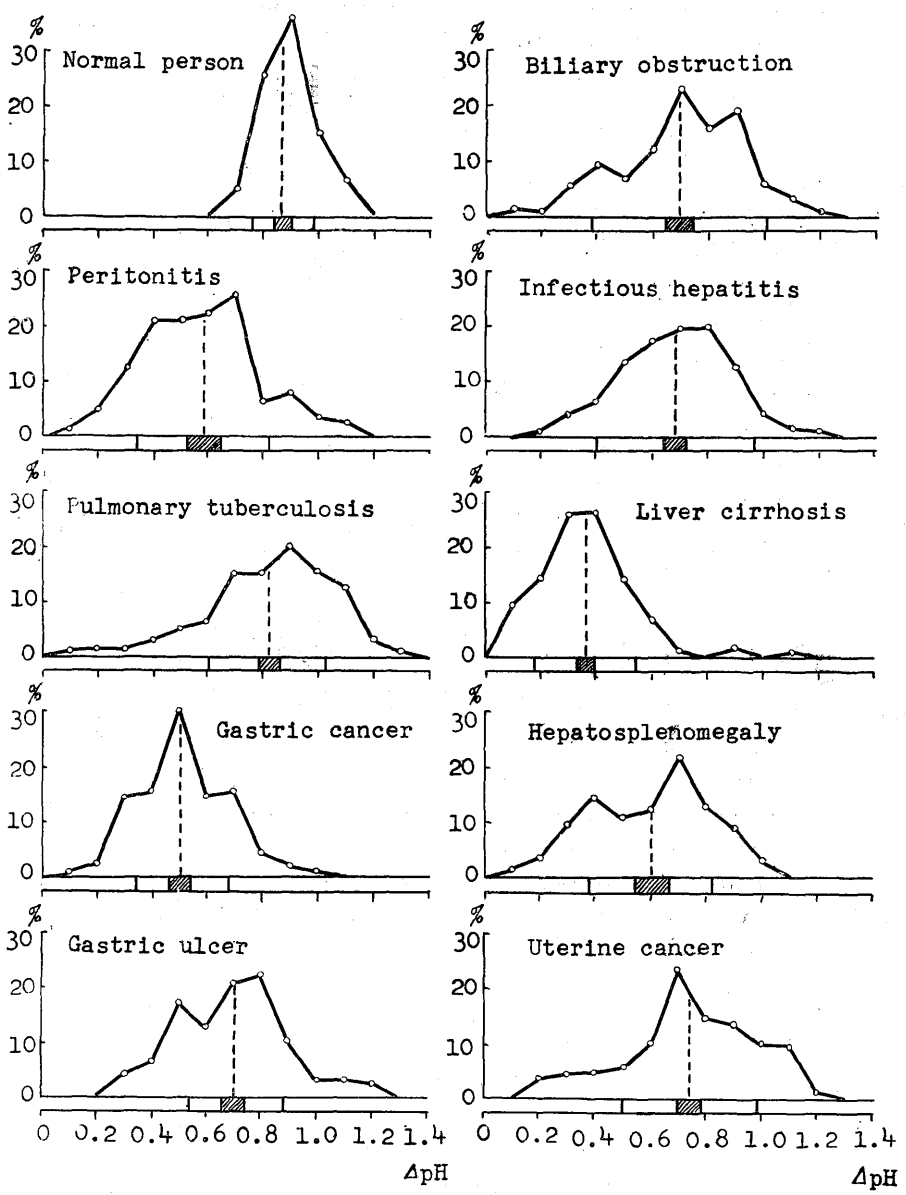

Fig. 5 Frequency distribution of serum cholinesterase in commonly encountered diseases.

Ordinate represens the frequency in per centage of total cases, and abscissa indicates the serum cholinesterase activity in ⊿pH. Confidence limits of the average and the rage of the average ± standard deviation were depicted for the purpose of comparison.

be revealed by the morphological study of the liver.

There seems to be little intimate correlationship between the reduction of serum cholinesterase activity and the presence of neoplastic process itself, since the activity varies greatly in the subnormal range, with the difference in the localization of the relevant neoplasm.

According to Vorhaus[4] the impaired function of liver resulting from hyperpyrexia and local anoxia is responsible for the diminished activity of serum cholinesterase in acute infection, but other factors are also supposed to be concerned in it, for acute hepatic diseases, for example hepatitis, scarcely entail a decrease as pronounced as that in acute infection.

In our study it was observed that serum cholinesterase exhibited conspicuous decrease in myelitis, gross lesion of spinal cord (trauma and tumor), uterine myoma, pemphygus and numerous other diseases with cause yet unknown.* Secondary hepatic disturbance is thought to be playing a considerable rôle, however.

It is obviously impossible to account for the reduction of serum cholinesterase activity in a variety of pathological conditions mentioned above by a universal principle. But there seems to be a considerably intimate correlation between the fall of serum cholinesterase activity and the chronic dysfunction of the liver, because diminution of the enzyme activity is common, as stated above, in the extra-hepatic diseases which are most likely to accompany the complication of hepatic dysfunction as well as in the hepatic diseases with anatomical lesion in the liver, for instance liver cirrhosis.

Increased activity of serum cholinesterase was unanimously confirmed in nephrosis (Type 2 Nephritis) by many authors[4,10,15,22], and our data also maintain their results. Opinions are, however, diversified upon the augmentation of the serum cholinesterase in diabetes mellitus[4,7-10], hyper tention[5-10,23], bronchial asthma[6,7,24,25] and hyperthyroisim[4,7,8,10,26], although in these conditions slightest increase was observed by our study. It will be interesting that the

* Greatness in the number of cases which were dealt with in our study contributed to the discovery of decreased serum cholinesterase in numerous kinds of diseasis. Relatively narrow range of normal activity of serum cholinesterase which was determined with strictly selected healthy persons as materials was likewise contributory to it. The range ΔpH 0,8-1.1 for normal serum cholinesterase[11] (Fig. 1) which forms a skew curve distribution with the average of ΔpH 0.87 was established by the examination of persons who showed normal pattern in the blood spectrum[27] (determination of seventeen chemical constituents of blood, including hemoglobin, hematocrit, serum protein, albumin, globulin, glucose, non-protein nitrogen, urea, ichteric index, bilirubin, alkaline phosphatase, inoganic phosphorus, amylase, cholesterol, phenol turbidity test, cephaline cholesterol flocculation and cholinesterase). Inasmuch as serum cholinesterase is frequently sensitive even to a minor disurbance in health, strict selection of healthy persons by systematic examination is supposed to be mandatory for the establishment of the normal range of this enzyme activity.

disputes about the change in serum cholinesterase are focused only upon the diseases which may entail increased activity.

The serum cholinesterase activity is generally normal in the diseases other than those already discussed upon[4-10].

Summary and Conclusion

Two thousand and eight hundred patients with various kinds of diseases was examined for serum cholinesterase activity by the phenol-red comparator method. The average activity (with confidence limit $\alpha=0.05$) as well as the standard deviation were calculated with regard to each kind of diseases to elucidate the aspect of pathological fluctuation of serum cholinesterase.

Serum cholinesterase decreased in hepatic diseases, diseases of the digestive tract, and neoplastic diseases. Among these, hepatic diseases, particularly liver cirrhosis, were remarkable and characteristic. Myelitis, trauma or tumor of the spinal cord (in advanced stage), septicemia, uterine myoma and pempygus entailed a similarly profound fall of serum cholinesterase. Accounting for the causation of decreased serum cholinesterase was beyond the scope of the present paper which did not aim at the study of the metabolism of serum cholinesterase. However, it seemed to be probable that hepatic disorders with or without anatomical lesion in the liver would be responsible for the reduction of this enzyme, at least in a considerable part.

Rise in serum cholinesterase was pathognomonic of nephrosis.

Grateful acknowledgements are due to Prof. Senji Uchino of the Department of Biochemistry, Kyoto University School of Medicine, for the preparation of manuscript, as well as to Prof. Susumu Shibata of the Department of Clinical Pathology, Yamaguchi Medical College, for his kind advice during the course of this study.

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