SERUM ENZYME ACTIVITY IN CHRONIC SCHIZOPHRENIA

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In recent years an ever-increasing interest has been taken in the possible use of serum enzyme investigations in clinical diagnosis, prognosis and therapy control. That clinical abnormalities are accompanied or even induced by biochemical aberrations is accepted. That the serum enzyme pattern may show consequent abnormality before the signs and symptoms familiar to the physician appear, has been also demonstrated in several disease states, such as caeruloplasmin in Wilson's disease (Scheinberg and Gitlin, 1952) and the transaminases in infective hepatitis (Wroblewski, 1957).

Following upon the neurological symptoms evinced in hepatolenticular degeneration and the fundamental part played by copper amine oxidase in this disease, the serum levels of caeruloplasmin in schizophrenia were investigated by Scheinberg and Morell (1957) and McDonald (1958). The transaminase activity in serum (Buscaino *et al.*, 1957; D'Argenio and Catalano, 1959), in cerebrospinal fluid (Rabassini and Chirillo, 1957) and lactate dehydrogenase in serum and cerebrospinal fluid (Fleisher *et al.*, 1957; Green *et al.*, 1958) have also been investigated in neurological diseases and schizophrenia. Juveth (1957) reported on serum aldolase activity in schizophrenias, and since the present study commenced, Plum (1960) has recorded serum pseudocholinesterase levels in mental and nervous disorders including 7 female schizophrenics. In a study of TPN linked enzymes in various disease states Kerppola *et al.* (1959) have reported on serum isocitrate dehydrogenase activity in 13 schizophrenic patients.

This paucity of references and the lack of detailed information regarding the state of the patients investigated prompted the present study of serum enzyme activities in patients suffering from chronic schizophrenia.

Methods and Materials

The clinical material consisted of 26 cases of chronic schizophrenia seen at Moorhaven Hospital and included 15 females with age range from 27 to 77 years and 11 males aged from 43 to 75 years. All cases were in-patients, fairly well adjusted to hospital life and easily managed by the staff. Duration of illness ranged from 4 to 48 years but at the time of the survey five females and one male were in remission. Only patients with definite signs and symptoms of schizophrenia were selected for this study. The diagnosis had been made by more than one doctor in the course of hospitalization. These diagnoses were thereafter reconsidered on the basis of their symptoms according to the criteria of Mayer-Gross, Slater and Roth (1960). Of the patients studied, one was diagnosed as catatonic, two as paranoid, two as hebephrenic and the remainder as chronic schizophrenia. The label "chronic schizophrenia" is given to patients whose

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symptoms varied in the course of their hospitalization and who therefore did not fit into only one schizophrenic sub-classification.

All patients had negative Wassermann tests and there was no suggestion that these patients were suffering from any acute or chronic physical illness either on admission or at the time of the test.

Blood for enzyme assay was collected without regard to fasting by venipuncture. The blood was allowed to clot, the serum separated as soon as practicable following centrifugation and stored at 4° C. until required for biochemical analysis. Serum showing visible haemolysis was discarded as erythrocytes are rich in some of the enzymes studied, particularly the dehydrogenases. No circumstance or condition was permitted which in our experience has been found to result in decrease or increase of serum activity of the enzymes studied. Patients had not received any drug treatment during the three days prior to bleeding except in one case where the patient had received 6 grains of sodium amytal the previous evening. No significant alteration in the levels of any of the biochemical parameters estimated was found in two healthy adult controls receiving the same treatment.

The serum enzymes studied in the survey were glutamate-oxalacetate transaminase (GO-T), glutamate-pyruvate transaminase (GP-T), lactate dehydrogenase (LDH), malate dehydrogenase (MDH), isocitrate dehydrogenase (ICD), pseudocholinesterase (pCE), aldolase (ALD), alkaline phosphatase (Al.P), and leucine aminopeptidase (LAP). GO-T and GP-T were assayed by procedures developed in the North Lonsdale Hospital laboratories (King, 1960a) as were LDH (King, 1959) and MDH (King, 1961). Isocitrate dehydrogenase activity was estimated by a method similar to that of Taylor and Friedman (1960) with a modified standard curve (King, 1960b). The procedures of Smith *et al.* (1959) for pCE, King and Wootton (1958) for Al.P and Goldberg and Rutenburg (1958) slightly modified for LAP, were used. The estimation of aldolase activity was performed by the Bruns (1954) modification of the method of Sibley and Lehninger (1949). All of these assay procedures are colorimetric and well suited to routine work or batch analysis. Total serum protein was estimated by a biuret procedure.

It has been customary in the past to express enzyme activity in units defined by each author and much confusion has resulted thereby. Recently a clinical Enzyme Sub-Commission has proposed the use of an International Unit (King and Campbell, 1960). This unit is defined as that which will transform one micromole of substrate per minute under the prescribed conditions of assay, activity to be expressed per litre. In this study all enzyme activities are expressed in International Units.

Results

A statistical analysis of the results obtained in this study together with normal values related to the assay procedures used is presented in Table I.

Twelve abnormal values were obtained in a total of 234 determinations consisting of elevation in pCE (5), Al.P (5), ICD (1) and LAP (1). Four patients had one, and four had two serum enzyme activities outside the usually accepted normal range, that is, approximately 30 per cent. of the series had abnormal serum enzyme patterns involving pCE, Al.P, ICD and LAP. However of the six cases in remission, four showed serum enzyme deviations and accounted for 6 of the abnormal levels. The only four high values obtained in females in the series were found in this group of symptomless schizophrenics. Three of the

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remaining elevated activities occurred in two male patients, both 75 years of age.

TABLE I

Serum Enzyme	Accepted Normal Range	Present Study: Range Encountered	Mean	Standard Deviation
GO-T ..	5 – 18	5·5– 15·1	10·2	±3·16
GP-T	4 – 16	4 – 12	8·35	±2
LDH ..	60 – 230	50 – 240	128·7	±49·4
MDH ..	10 – 44	10 – 41 (omitting single value of 15·3)	24·8	±8·8
ICD	2 – 8·5	2 – 8·1	4·06	±1·44
pCE	3,300 –7,100	3,900 –8,700	6,012	±1,410
ALD ..	2 – 6	1·8–5·4 (omitting single value of 310)	3·4	±1·5
Al.P. ..	30 – 85	27·5– 115 (omitting single value of 66)	60·5	±23·66
LAP	15 – 50	21 – 46	33·25	±7·2
Total serum protein (g./100 ml.)	6·3– 8·2	6·5– 9·0	7·4	±0·54

All figures for enzyme activities are expressed in International Units (I.U.)

DISCUSSION

GO-T and GP-T are enzymes which provide a link between protein and carbohydrate metabolism and have been widely studied in clinical medicine in recent years. LDH and ALD are glycolytic enzymes while MDH and ICD are biocatalysts of the Krebs' tricarboxylic acid cycle. Esterases are represented in the present study by pseudocholinesterase and alkaline phosphatase. LAP is a peptidase which has received attention in diseases involving the liver and pancreas.

Variation in some enzyme activities with sex and age have been reported, but Antebi and King (1958) found no significant difference in GO-T and GP-T with either sex or age and it is our experience with the enzymes presently under investigation that any alteration of enzyme activity with age or difference in serum levels between the sexes is without significance and no cognition otherwise has been given in this survey.

The effects of various forms of chemotherapy on serum enzyme activity are much more remarkable and have been the subject of various reports (Wroblewski, 1957; Foulk and Fleisher, 1957; Wroblewski and Manso, 1958). It is considered essential that cases to be studied should not be on a drug regimen or where this is not practicable that controls should be investigated to determine whether the therapeutic agent causes any serum enzyme deviation. In the present study every effort was made to adhere to this principle. Plum (1960) did not consider that chemotherapy altered pseudocholinesterase activity but it is interesting to note that Osmond and Hoffer (1959) report that this enzyme is preferentially blocked by the hallucinogenic drug LSD-25. Juveth (1957) recognized the possible alteration in serum enzyme levels caused by drugs; other authors have failed to record data on this point and often on the state of the patients.

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The results obtained tend to show that activity of GO-T, GP-T, LDH, MDH, ICD, ALD and LAP are essentially the same as would be expected from a similar group of healthy adults and for ALD, LDH and ICD this is in agreement with earlier authors. The figures obtained for GP-T are not necessarily in disagreement with the report of Rabassini and Chirillo (1957) of increased GP-T activity in the cerebrospinal fluid of schizophrenics, as the blood-brain barrier is impermeable to the enzyme protein.

Buscaino *et al.* (1957) reported an increase in serum α-oxoglutaric acid in schizophrenia with an inversion of the ratio GO-T/GP-T. Antebi and King (1958) in a survey of 150 healthy adults gave normal values for this ratio as 0·89 to 3·57. An analysis of the figures obtained in the present study gives a range of 0·58 to 3·0 with a mean of 1·3 and a standard deviation $\pm 0{\cdot}5$. These figures are lower than normal but the overlap of the ranges negates any clinical significance, and this is in agreement with the findings of D'Argenio and Catalano (1959).

The increased activity of pCE found in this study is in partial agreement with Plum (1960) but it must be emphasized that three of the five abnormally high levels were found in patients in remission or symptomless. Indeed, despite the fact that approximately 30 per cent. of the patients in this series had deviations of at least one of the serum enzymes studied, no diagnostic significance attaches to any of the nine enzymes assayed. There was no correlation between enzyme abnormality and clinical state, age, sex or other condition.

In another series of six patients with an acute schizophrenic process no consistent abnormality was disclosed by estimation of the same enzymes.

A search of the literature does not reveal any previous reference to serum activities of MDH, Al.P or LAP in schizophrenia.

It is known that some diseases such as galactosaemia, gargoylism and phenylpyruvic amentia are due to enzyme abnormalities. Saunders (1957) thinks that psychosis is caused by unsatisfactory chelation resulting in an imbalance between the deamination and transamination oxidases, and aberrant oxidative phosphorylation. It is possible that further study of other serum enzymes along these lines might be more rewarding. However, intracellular enzyme disturbances may occur without influencing the serum enzyme levels unless there is simultaneous increased permeability of the cell to the enzyme protein, activator or inhibitor, whichever is the cause of the abnormality. Even where an intracellular enzyme deviation results in liberation of enzyme or inhibitor into the circulation, the wide normal range in many cases could readily mask small increases or decreases and render assay of the biocatalyst of no clinical significance.

Summary

The serum activities of nine enzymes, glutamate-oxalacetate transaminase (GO-T), glutamate-pyruvate transaminase (GP-T), lactate dehydrogenase (LDH), malate dehydrogenase (MDH), isocitrate dehydrogenase (ICD), pseudocholinesterase (pCE), aldolase (ALD), alkaline phosphatase (Al.P) and leucine aminopeptidase (LAP) have been assayed in a series of 26 cases of chronic schizophrenia.

Two cases, one in remission, showed simultaneous elevated pCE and Al.P activity; one patient had concomitantly elevated Al.P and ICD levels and another Al.P and LAP activities. One more patient had a high Al.P level and three had elevated pCE activity.

No symptoms of other disease were evinced by any of these patients

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showing abnormal enzyme levels and it is difficult to offer an explanation of these findings as there was no correlation between serum enzyme abnormality and clinical state or age.

It would appear that estimation of any of the enzymes studied holds no diagnostic value in chronic schizophrenia.

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REFERENCES

ANTEBI, R. N., and KING, J., *Lancet*, 1958, *i*, 1133.
BRUNS, F., *Biochem. Ztschr.*, 1954, **325**, 156.
BUSCAINO, V. M., *et al.*, *Acta Neurol.*, 1957, **12**, 446.
D'ARGENIO, L., and CATALANO, V., *Riv. Pat. nerv. ment.*, 1959, **80**, 281.
FLEISHER, G. A., WAKIM, K. G., and GOLDSTEIN, N. P., *Proc. Staff Meet. Mayo Clin.*, 1957 **32**, 188.
FOULK, W. T., and FLEISHER, G. A., *ibid.*, 1957, **32**, 405.
GOLDBERG, J. A., and RUTENBURG, A. M., *Cancer*, 1958, **11**, 283.
GREEN, J. B., OLDEWURTEL, H. A., O'DOHERTY, D. S., and FORSTER, F. M., *Arch. Neurol. and Psychiat.*, 1958, **80**, 148.
JUVETH, L., *Ztschr. klin. Med.*, 1957, **154**, 569.
KERPPOLA, W., NIKKILA, E. A., and PITKANEN, E., *Acta Med. Scand.*, 1959, **164**, 357.
KING, E. J., and CAMPBELL, D. N., *4th International Congress on Clinical Chemistry, Edinburgh*, 1960.
Idem and WOOTTON, I. D. P., *Micro-analysis in Medical Biochemistry*, 1958. London: Churchill.
KING, J., *J. med. Lab. Technol.*, 1959, **16**, 265.
Idem, *ibid.*, 1960a, **17**, 1.
Idem, *ibid.*, 1960b, **17**, 89.
Idem, *ibid.*, 1961, **18**, 168.
MAYER-GROSS, W., SLATER, E., and ROTH, M., *Clinical Psychiatry*, 2nd Ed. 1960. London: Cassell & Co. Ltd.
MCDONALD, R. K., *J. chron. Dis.*, 1958, **8**, 366.
OSMOND, H., and HOFFER, A., *J. Ment. Sci.*, 1959, **105**, 440.
PLUM, C. M., *Clin. Chem.*, 1960, **6**, 332.
RABASSINI, A., and CHIRILLO, R., *Acta vitamin.*, 1957, **11**, 197.
SAUNDERS, G. C., *Chemical Concepts of Psychosis* (Rinkel, M.), 1957. London: Peter Owen, 1960.
SCHEINBERG, I. H., and GITLIN, B., *Science*, 1952, **116**, 484.
Idem and MORELL, A. G., *ibid.*, 1957, **126**, 925.
SIBLEY, J. A., and LEHNINGER, A. L., *J. biol. Chem.*, 1949, **177**, 859.
SMITH, R. L., LOEWENTHAL, H., LEHMANN, H., and RYAN, E., *Clin. chem. Acta.*, 1959, **4**, 384.
TAYLOR, T. H., and FRIEDMAN, M. E., *Clin. Chem.*, 1960, **6**, 208.
WROBLEWSKI, F., *Hepatitis Frontiers*, 1957. Boston: Little, Brown & Co.
WROBLEWSKI, F., and MANSO, C., *J. Amer. med. Ass.*, 1958, **167**, 2163.

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