SERUM LACTIC DEHYDROGENASE AND RIBONUCLEASE IN THE DIAGNOSIS OF MALIGNANT TUMOURS IN CHILDREN*

BY

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In recent years increasing attention has been given to the fluctuations of serum enzymes in neoplastic disease. It is thought that increased activity of certain enzymes in cancer cells and in damaged tissues results in the release of enzymes into the serum. Among many enzymes that have recently received interest, in relation to malignant neoplasia, are *lactic dehydrogenase* (SLD) (Wróblewski, 1957, 1959; Blanchaer, Green, Maclean, and Hollenberg, 1958) and *ribonuclease* (RN-ase) (Wróblewski, 1961).

In 1930 Warburg, while investigating the metabolism of neoplastic tissue, showed that in carcinomatous cells respiration was irreversibly impaired, with the consequence that there was increased anaerobic glycolysis. In spite of Warburg's discovery it was not until 1954 that Hill and Levi showed that the activity of lactate dehydrogenase, the end-enzyme of anaerobic glycolysis, rose in the serum of some patients with neoplastic disease.

At present SLD activity seems to be a factor of some importance in the biochemical diagnosis of malignant neoplasia in adults (Wróblewski, 1961). Unfortunately, SLD can also be influenced by disease states other than malignant neoplasia, nor is its activity always increased in cancer (Zimmerman and Weinstein, 1956).

No data are available on SLD activity in children with malignant tumours, though the problem merits special attention since lactic dehydrogenase activity in tissues of the foetus and newborn is much higher than in adults. LD is a soluble enzyme located primarily in cytoplasm, so it would enter the blood more readily than would the insoluble enzymes located in mitochondria. Taking into consideration the high LD activity in young cells, one would expect SLD to be a much more sensitive index of neoplastic processes in newborns and very young children than in adults.

Available data on serum RN-ase activity mainly

concern different forms of leukaemia in adults, and the results are contradictory (Wróblewski, 1961; Aleksandrowicz, Urbanczyk, Ostrowska, and Sierko, 1958). Since this enzyme is connected with cellular nuclei, the enhanced activity in serum should reflect a tissue breakdown and might be of importance in cancer detection.

In this paper an attempt is made to find out how far changes in serum activity of these two enzymes may be useful in the early diagnosis of congenital neoplasia.

Material and Methods

As there are many conflicting reports of normal values for SLD (Rapp and Bell, 1961), we have established normal values for healthy children. The control group of healthy children was divided into three age-groups: 0-2, 2-7, and 7-14 years. Normal values for RN-ase activity in serum were determined for the same age-groups.

As well as cases with malignant neoplasia, a small group of benign tumours comprising cases of haemangioma was studied.

The blood for SLD and RN-ase activity determinations was drawn by venepuncture and the serum separated. For SLD determination sera were stored frozen for periods not exceeding 3 days. RN-ase activity assays were performed only in fresh sera. The method used for SLD determination was that of Cabaud and Wróblewski (1958). RN-ase activity was determined according to Métais and Mandel (1955).

Results

The values obtained for SLD and RN-ase activity in healthy children are listed in Table 1.

The highest SLD activity was observed in the age-group 0-2 years, the mean value for this group being significantly higher than those for older children and for adults. By contrast, serum activity of RN-ase rises with the child's age, the differences in mean values for each age-group being significant.

The activity of the two enzymes in cases of malignant neoplasia is shown in Table 2. Except

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TABLE 1
NORMAL RANGES FOR LEVELS OF SERUM LACTIC DEHYDROGENASE AND RIBONUCLEASE IN CHILDREN

Age-group (yr.)	Lactic Dehydrogenase			Ribonuclease		
	Number	Range (units)	Mean Value (units)	Number	Range (units)	Mean Value (units)
0-2	14	290-540	431	8	54-206	139
2-7	25	250-515	392	15	74-260	163
7-14	18	240-460	380	24	97-244	190
Adults	21	212-423	320			

TABLE 2
SERUM LACTIC DEHYDROGENASE (SLD) AND RIBONUCLEASE (RN-ASE) ACTIVITY IN 20 CASES OF MALIGNANT NEOPLASIA IN CHILDREN

Case No.	Diagnosis	Age (yr.)	SLD Level (units)	RN-ase Level (units)
1	Malignant hepatic tumour	1		175
2	Wilms' tumour	1		191
3	Eosinophilic granuloma of skull and clavicle: multiple metastases	2		190
4	Nephroblastoma	6		148
5	Agranulocytosis	13		134
6	Glioma	4	660	
7	Nephroblastoma	4	950	
8	Nephroblastoma	5	690	
9	Nephroblastoma	5	1040	
10	Nephroblastoma	2	800	
11	Ovarian tumour	4	1220	
12	Nephroblastoma	6	860	
13	Thyroid carcinoma	7	980	
14	Nephroblastoma	9	830	
15	Sarcoma	3	1120	
16	Glioma	5	815	
17	Malignant bone tumour	8	880	
18	Hepatoblastoma	14	460	
19	Neuroblastoma	2	1015	
20	Thyroid carcinoma	3	634	

in one case of hepatoblastoma, SLD activity is higher than in controls. RN-ase level shows no such trend.

In a group of 7 (benign) haemangiomas the mean values for SLD amounted to 455 units, which does not differ statistically from the control group.

Discussion

SLD was found to be raised in almost all cases of malignant neoplasia in this study. This result differs from those reported for neoplastic diseases in adults (Wróblewski, 1957, 1959; Blanchaer *et al.*, 1958; Zimmerman and Weinstein, 1956), where SLD is increased in only about 50% of cases of various neoplasia. Wróblewski (1961) states that SLD activity in adults may contribute to the diagnosis of neoplasia in three clinical situations—disseminated cancer, lymphoma, and myelogenous leukaemia. Our results show that in children SLD activity increased in malignant neoplasia, independently of the origin of the tumour in almost 100% of cases.

In the only case, that of a hepatoblastoma, with a normal value for SLD, bilirubin may have interfered with the estimation of enzyme activity, as in this case jaundice was severe. The more consistent increase in SLD in neoplasia in children, when compared with findings in adults, is presumably the result of the increased metabolism in children. This is especially evident when comparing normal values for SLD at different age-groups. The highest mean value is for newborns, where some residue of foetal anaerobic metabolism is still present. Increased glycolytic activity of tumours seems to be more prominent in children than in adults, resulting in leaking of the enzyme into the serum. Due to the cytoplasmic, extra-mitochondrial site of LD, such leakage can take place before the breakdown of tissues, which is a factor of importance in the early diagnosis of neoplastic disease.

The absence of any increase in SLD in the benign neoplasia (haemangiomas) that we tested supports the significance of raised SLD levels in malignant neoplasia.

There are also certain non-neoplastic states associated with increased SLD, e.g. myocardial infarction, hepatitis, some haemolytic states, dermatomyositis, and muscle trauma.

Serum RN-ase activity appeared to be slightly raised only in a few cases of malignant neoplasm in children. This increase might be due to the tissue damage that takes place in advanced neoplastic disease. If so, an increased activity of RN-ase in serum might be an index of necrotic changes during the development of malignant tumours.

Summary and Conclusions

Serum lactic dehydrogenase activity rises up to three times normal values in almost 100% of cases of malignant tumours in children. SLD level increases in every case of disseminated cancer. Hence it can be a factor of importance in the prognosis and diagnosis of neoplastic diseases in children, especially in the age-group 0-2 years. Ribonuclease activity in serum does not give as distinct a picture of neoplastic disease as SLD does.

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