increased plasma enzyme levels² and it has become common practice to regard plasma LDH₁ and LDH₂ values as an index of ineffective erythropoiesis in other haematological disorders.

Recently developed techniques allow the amount of ineffective iron turnover in the marrow to be measured. Turnover is greatly increased in those conditions, particularly megaloblastic anaemia and homozygous β -thalassaemia, where ineffective erythropoiesis is a prominent feature, and its measurement gives a quantitative assessment of the destruction of erythroblast cytoplasm. We compared ineffective iron turnover with the serum activity of LDH₁ and LDH₂ measured specifically as 2-hydroxybutyrate dehydrogenase (HBD) activity in patients with megaloblastic anaemia and in several other haematological disorders.

Patients, methods, and results

Fully informed consent was obtained from each of the 29 patients who took part in this study. Six had megaloblastic anaemia as a result of either folate or vitamin B₁₂ deficiency; their haemoglobin concentrations ranged from 5.5 to 8.3 g/dl and they had a mean cell volume of 121-139 fl. Five patients had heterozygous β -thalassaemia with a haemoglobin concentration of 10.5-13.5 g/dl; haemoglobin A₂ was 3.9-7.4% and haemoglobin F was 0.9-2.4%. Seven patients were suffering from homozygous β -thalassaemia and required regular blood transfusions; at the time of the investigation their haemoglobin concentrations were 9.1 and 13.2 g/dl. Five patients had an anaemia that was refractory to haematinic treatment and resulted from neither an identifiable genetic defect nor malignancy. Haemoglobin concentrations in these patients ranged from 6.6 to 12.6 g/dl and four of them were receiving regular blood transfusions. Six patients had iron deficiency anaemia with haemoglobin concentrations of 7.1-9.9 g/dl and a serum ferritin concentration of less than 10 μ g/l. Ineffective iron turnover was derived from the plasma ⁵⁹Fe clearance curve over 14 days.³ Serum for 2-hydroxybutyrate dehydrogenase (HBD) assay was obtained from a clotted venous blood sample. Contaminating red cells were removed by centrifuging twice at 300 g for 15 minutes.

In the patients with megaloblastic anaemia both the HBD levels and the ineffective iron turnover were greater than normal (see figure), and there was a clear relationship between ineffective iron turnover and HBD. By contrast, the HBD levels remained essentially normal in other patients in whom ineffective iron turnover was also considerably increased. One of the patients with iron deficiency anaemia had a serum HBD concentration greater than 500 IU/l yet both he and the other anaemic patients had ineffective iron turnover within the normal range.

Serum HBD and ineffective iron turnover in (a) patients with megaloblastic anaemia (●) ($r=0.84$; $t=3.14$; $P<0.05$); (b) patients with iron deficiency anaemia (○), refractory anaemia (▲), heterozygous β -thalassaemia (□), or homozygous β -thalassaemia (■).

Dotted lines show normal upper limit for each value: SHBD—350 IU/l; ineffective iron turnover—54 μ mol/l blood/day.

Comment

This study shows that the increased serum HBD activity in patients with megaloblastic anaemia is related to ineffective erythropoietic iron turnover and supports the suggestion⁴ that the serum enzyme is derived from the destruction of megaloblast cytoplasm. In other conditions where ineffective erythropoiesis is known to be increased the serum HBD level was not increased even though ineffective iron turnover in these patients was up to 20 times the normal level and was similar to that found in the megaloblastic patients. Both we and others⁵ have, however, found increased serum HBD concentrations (up to 2300 IU/l) in patients with intravascular, but not intramedullary, haemolysis. Our results show that serum HBD activity cannot be used as an index of ineffective erythropoiesis in disorders other than megaloblastic anaemia.

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Effect of chlormethiazole on serum prolactin

Chlormethiazole edisylate, 5-(2-chloroethyl)-4-methylthiazole ethane-disulphonate, is chemically related to the thiazole nucleus of the thiamine (vitamin B₁) molecule. It is a central nervous system depressant, probably acts on the cortex, and has an early sedative, hypnotic effect. It is widely used to counter the alcohol withdrawal syndrome, including delirium tremens, and to treat psychomotor agitation, anxiety-tension states, sleep disturbances, and also status epilepticus. A wide variety of structurally unrelated drugs including tranquillisers are known to interfere with serum concentrations of prolactin.^{1,2} We report the effect of chlormethiazole on serum prolactin levels in 16 male alcoholics.

Patients, methods, and results

Sixteen male chronic alcoholics in hospital (mean age 43.4 ± 2.6 SEM) with normal serum prolactin concentrations were included in the study. Three (patients 4, 11, and 16) were found on liver biopsy to have steatosis. None of the patients showed clinical or biochemical evidence suggestive of cirrhosis. All totally abstained from alcohol during the period of the study. All blood samples were collected at the same time of the day and under identical conditions. Serum prolactin concentrations were measured by radioimmunoassay at the time of admission and again after treatment (seventh day). No patient suffered from a malabsorption syndrome or any other condition known to interfere with serum prolactin concentrations, and there was nothing to suggest that absorption of drugs by mouth was impaired. The data were analysed by Student's *t* test.

All patients were given our routine detoxification treatment for alcoholism. This includes the following drugs: (1) chlormethiazole edisylate (Heminevrin capsules 500 mg, 192 mg base per capsule), three capsules thrice daily for three days, two capsules twice daily for two days, and one capsule thrice daily for one day—a total, on average, of 42 capsules (8.064 g of chlormethiazole base) over six consecutive days; (2) intravenous Parentrovite (high potency) 10 ml daily for five days.

The mean ($\pm$ SEM) serum prolactin concentration on admission was

Serum prolactin (PRL) concentrations before and after treatment

Patient No	Age (y)	Serum PRL (mU/l)*	
		Before	After
1	41	330	310
2	35	350	190
3	29	280	140
4	47	180	130
5	35	180	180
6	53	330	250
7	53	330	130
8	47	250	120
9	42	390	180
10	44	280	280
11	56	140	110
12	31	280	150
13	53	220	170
14	29	270	150
15	37	260	210
16	63	440	90
Mean ($\pm$ SEM)	43.4 ($\pm$ 2.6)	281.9 ($\pm$ 19.9)	174.4 ($\pm$ 15.5)

*Normal = up to 500 mU/l.

281.9 mU/l $\pm$ 19.9 (table). It fell to 174.4 mU/l $\pm$ 15.5 after treatment. This difference was highly significant ($t=3.04$; $0.01 > P > 0.001$).

Comment

The serum prolactin concentration in man is largely controlled by hypothalamic prolactin inhibitory factor, which is related to dopamine and, indeed, may itself be dopamine. To a lesser extent the concentration is controlled by prolactin releasing factor, which is also hypothalamic in origin, is probably a polypeptide, and its secretion may depend on serotonin acting as an intrahypothalamic neurotransmitter.^{1,3} Many structurally unrelated and pharmacologically diverse drugs that act on the central nervous system interfere with the secretion or release, or both, of prolactin, thereby causing hyper- or hypoprolactinaemia. Hyperprolactinaemia is caused by phenothiazines, butyrophenones, tricyclic antidepressants, metoclopramide, sulpiride, reserpine, methyl dopa, oestrogen, thyrotrophin-releasing hormone, chlorthalidoxepoxide, D-amphetamine, and antihistamines (meclozine and tripeleminamine).^{1,2,4} Hypoprolactinaemia is caused by dopamine agonists such as bromocriptine, by dopamine replenishing agents—for example, levodopa—by monoamine oxidase inhibitors (iproniazid, pargyline), and also by clonidine.²

Clearly many drugs that act on the central nervous system interfere with prolactin secretion or release, thereby altering serum concentrations. Chlormethiazole seemed to lower the prolactin level in our patients to a statistically significant extent. In this respect it differs from other tranquillisers such as phenothiazines and at least some of the benzodiazepines. Chlormethiazole might therefore be valuable in treating hyperprolactinaemia. We cannot explain the mechanisms involved, but perhaps chlormethiazole interferes with the intrahypothalamic neurotransmitters (dopamine and serotonin) that regulate prolactin release or secretion, or both. Further work is in progress.

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Diabetes mellitus in idiopathic haemochromatosis

Diabetes mellitus in patients with idiopathic haemochromatosis (IH) is widely believed to be due to islet cell destruction by iron. This view has recently been challenged, and it has been suggested that diabetes associated with IH may be of genetic or multifactorial origin.^{1,2} We investigated this question by studying α -cell responses in patients with diabetes and IH. In idiopathic diabetes plasma pancreatic glucagon concentrations rise after arginine stimulation. By contrast, in diabetes secondary to chronic pancreatitis or transfusional haemosiderosis glucagon responses are impaired.³ If diabetes associated with IH results from islet cell damage, glucagon responses would be expected to be impaired.

Patients, methods, and results

Ten patients aged 55 to 79 years with diabetes and IH were investigated. They had had diabetes for 1 to 23 years and IH for 1 to 16 years. Five of the eight patients tested were HLA type A3B7. Six were on insulin, three on oral hypoglycaemic agents, and one on diet alone. All had undergone

Mean blood glucose and pancreatic glucagon concentrations in patients with IH and controls.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Glucagon: 1 pmol/l $\approx$ 3.48 ng/l.

venesection and at the time of study the serum iron concentration was raised in three patients. Nine patients with idiopathic diabetes matched for sex, age, duration of diabetes, treatment, and percentage ideal body weight were controls. A standard arginine stimulation test was carried out in the fasting state. Venous samples were withdrawn for measurement of blood sugar and plasma glucagon (SRB).

The mean blood sugar values for the patients with IH did not differ significantly from those of the controls ($P > 0.05$). The basal glucagon values were similar in both groups, and after arginine infusion plasma glucagon concentrations showed the expected rise in the controls. In the patients with IH the concentrations also rose, being significantly higher than control values at 15 minutes ($P < 0.05$).

Comment

That diabetes associated with IH results from islet cell damage by iron is supported by reports of a high incidence of diabetes in patients with IH² and the reduction in insulin dose in some patients after venesection. That the diabetes is not due simply to iron deposition, however, is suggested by the high incidence of diabetes in relatives of patients with IH with normal iron stores^{1,2}; observations that after iron depletion carbohydrate metabolism is sometimes unaltered or even deteriorates; and the poor correlation between the degree of iron overload and the presence of diabetes.¹