Iron granules in plasma cells

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SUMMARY The curious and unusual finding of coarse iron granules in marrow plasma cells is reported in 13 patients, in whom the finding was incidental. In 10 of these patients there was known alcohol abuse and serious medical complications of that abuse. Previous reports of the finding are reviewed. Haematological data of the 13 patients are presented. A hypothesis is outlined which may account for the finding.

Iron in plasma cells has been recorded by several authors. Koszewski¹ in 1952 described nine patients with haemochromatosis, megaloblastic anaemia and excess iron in marrow macrophages and also showed accumulation of iron in plasma cells. All nine patients had alcohol problems. The authors commented that in haemochromatosis without megaloblastic anemia, iron in plasma cells was seldom seen. They concluded that in conditions of increased haemosiderin deposition, such as the combination of haemochromatosis and megaloblastosis, the capacity of the marrow for storage was overwhelmed and disposal had to take place where it could—that is, in plasma cells which were thought to phagocytose the material.

Goodman and Hall² referred to the finding of iron in plasma cells by a number of workers, added four patients and performed electron microscopy. Their patients had respectively haemochromatosis, megaloblastic anaemia, refractory normoblastic anaemia and porphyria cutanea tarda. Electron microscopy showed the iron to be in single-membrane vesicles between the Golgi apparatus and the endoplasmic reticulum, and adjacent to mitochondria. They discussed the possible modes of entry of iron into the cell and concluded that surface absorption of iron from transferrin was the most likely mechanism. The rôle of the iron in this site was difficult to determine and they felt that storage was unlikely. The features of these plasma cells, namely prominent endoplasmic reticulum, large Golgi bodies and many mitochondria, suggested a relation of the iron to protein synthesis.

Lerner and Parker³ described an 81-year-old patient with a monoclonal IgG band in the plasma, with no evidence of multiple myeloma in the marrow,

but who had iron inclusions in plasma cells. Electron microscopy showed features similar to those described by Goodman and Hall² but the vesicles were thought to be lysosomes. A single intravenous injection of ⁵⁹Fe was given and radioactivity was demonstrated by autoradiography in plasma cells within one day of injection. It was still present next day. This speed suggested incorporation of iron by a more direct mechanism than phagocytosis.

Iron-containing granules have also been found in plasma cells at the site of a healed spider bite⁴ and presumed to be related to local iron excess, accumulated as a result of haemorrhage and necrosis.

In 1978 Karciglu and Hardison⁵ described 21 anaemic, alcoholic patients admitted with the complications of alcoholism, whose marrow plasma cells contained iron. They considered that this was a regular finding in disease with iron overload or defective utilisation of iron by red cells, and was especially found in anaemic alcoholic patients. They did not cast any further light on the origin of the iron granules.

In 1979 Shanmugathasa *et al*⁶ described a further alcoholic patient with severe, megaloblastic, folate-responsive anaemia, whose marrow plasma cells contained iron granules. They demonstrated by electron microscopy close proximity of the plasma cells to iron-rich reticulo-endothelial phagocytic cells, with cytoplasmic bridges between the cells. They thought iron could be transferred along these cytoplasmic corridors to plasma cells. They also demonstrated micropinocytotic vesicles incorporating ferritin granules.

The recurring reference to alcoholic patients in the above reports is noteworthy. However there is no concerted opinion as to how the iron comes to be in the plasma cells, or what purpose, if any, it serves there.

Patients and methods

Approximately 1000 bone marrow aspirates were examined routinely between April 1975 and May 1980 by one of us (MKC). These were stained by the May-Grünwald-Giemsa (MGG) method, and by Perls' Prussian blue (PPB) method with neutral red counterstain.

A small number of marrows had shown inclusions in plasma cells, staining yellow-brown in MGG, and blue in PPB stains. It was concluded that these granules were iron-containing. This observation was recorded each time it was made on a routine marrow sample. The marrows were re-examined in June 1980. The finding of iron-inclusions in plasma cells was confirmed. An attempt to quantify the abnormal finding was made by counting 50 plasma cells in each case and calculating the percentage of plasma cells positive for inclusions (although in one case only 20 cells could be counted). This percentage assessment was made on the PPB stain with neutral red counterstain, on which the plasma cells were readily identified and distinguished from other cells.

Even in the oldest marrows (5 years old), in which there had been some fading of the counterstain, plasma cells were identifiable.

The percentage of plasma cells in each marrow was estimated by counting 500 cells on an MGG stain. A subjective assessment of the quantity of iron in the whole marrow and in individual plasma cells was also made (Table 1). Clinical details of the patients from whom the marrows had been taken were assessed from the case notes.

An attempt was made to compare a control group of patients with the above. The names of 13 age- and sex-matched patients, who had had marrow aspirates during the same period, in which the plasma cells were found not to carry iron, were extracted at random from the marrow report filing system. Their case notes were also examined.

Results

All patients had plentiful iron in their marrows, which was quantitatively within normal limits in all except three patients in whom it was increased.

Table 1 Details of plasma cells and iron content of marrows

Patient	Age	Sex	% plasma cells in marrow. 500 cell count. MGG stain. Normal < 4%	Quantity of marrow-iron stores (subjective assessment on PPB stain)	Numbers and % of plasma cells with iron. 50 cell count. PPB stain			Form of iron in plasma cells	Other marrow abnormalities
					Pos	Neg	%Pos		
1	40	M	< 1	Normal	13	7	65	Multiple coarse granules	Megaloblastic and sideroblastic
2	47	F	2	Normal	47	3	94	Multiple coarse granules, some plaques	Megaloblastic with non-ring sideroblasts
3	83	M	2	Normal	26	24	52	Multiple coarse granules	Megaloblastic with non-ring sideroblasts
4	63	F	< 1	Normal	41	9	82	Multiple coarse granules	Megaloblastic with non-ring sideroblasts
5	55	M	1	Normal	47	7	86	Multiple granules occasional plaques	Megaloblastic with non-ring sideroblasts
6	55	F	1	Increased	31	19	62	Multiple coarse granules (up to 22) and plaques	Megaloblastic and sideroblastic
			1.5	Normal	11	39	22	Less than 6 coarse granules; no plaques	Megaloblastic dysplasia non-ring and occasional ring sideroblasts
7	50	M	12	Increased	18	32	36	Multiple coarse granules	Reactive features. Mild megaloblastic change. No sideroblasts
8	78	F	4	Normal	21	29	42	Fine granules	Megaloblastic with non-ring sideroblasts
9	44	F	4	Normal	30	20	60	Coarse granules occasional plaques	Megaloblastic and sideroblastic
10	81	F	4	Increased	36	14	72	Multiple coarse granules and plaques	Gross sideroblastic change
11	69	M	1	Normal	26	24	52	Multiple coarse granules; some plaques	Megaloblastic change with non-ring sideroblasts
12	64	F	6.5	Normal	28	22	56	Multiple coarse granules; some plaques	Megaloblastic change with non-ring sideroblasts
13	51	M	1.5	Normal	27	23	54	Multiple coarse granules; some plaques	Micronormoblastic; iron only in plasma cells

Table 1 gives details of iron distribution in the marrows. In general any plasma cell in an affected marrow either contained a heavy load of iron or none at all. In some plasma cells there was a tendency for the granules to coalesce into plaques (Figs. 1 and 2).

Four patients showed ring sideroblast formation. Two of these also had increased iron and three of

these had the lowest admission haemoglobin of all 13 patients; Table 2 gives other haematological details and diagnoses.

One patient who had increased marrow iron and a particularly heavy load of iron in some of her plasma cells, had a repeat marrow six weeks after the first. The total quantity of iron in the second marrow appeared normal and the iron load of individual plasma cells was considerably reduced (Table 1). Apart from this observation there is no obvious direct correlation between quantity of storage iron, percentage of iron-loaded plasma cells and individual iron load of plasma cells.

Except in 2 patients (cases 7 and 12) plasma cells were not increased. The former was known to have active inflammatory disease which was probably related. All marrows, except that of case 13, showed megaloblastic or sideroblastic change or both.

Case 13 was of particular interest in that he had a blood picture suggestive of iron deficiency, with an MCV of 79 fl, MCH of 24 pg and hypochromic, microcytic cells in his blood film. Erythropoiesis showed micronormoblastic maturation with karyorrhexis. Serum iron was reduced and iron-binding capacity increased giving a saturation of iron-binding capacity of only 3% (Table 2). Serum ferritin was normal however, at 153 $\mu\text{g/l}$ (normal = 50-267 $\mu\text{g/l}$). Beta-thalassaemia trait was unlikely as he had had a normal blood count and film four years previously. Moreover he was losing significant amounts of blood in his urine from a bladder carcinoma. Yet this patient had normal quantities of iron in his marrow. Nevertheless the only cells which could be clearly identified in the marrow as iron-carrying were plasma cells. It seems that the

Fig. 1 Case 13, Marrow plasma cell showing multiple coarses granules which are tending to coalesce into plaques. May-Grünwald-Giemsa stain $\times 13\ 500$

Fig. 2 Case 13, Marrow plasma cell showing a large plaque. The proximity of an erythroblast shows that the two types of cell are readily distinguished even without the benefit of staining characteristics. May-Grünwald-Giemsa stain $\times 13\ 500$

Table 2 Haematological details and diagnoses

Patients	Hb (g/dl)	MCV (fl)	Serum folate (µg/l)	Serum B ₁₂ (ng/l)	Red cell folate (µg/l)	Serum iron (µmol/l)	Iron/binding capacity (TIBC) (µmol/l)	% saturation of TIBC	Clinical diagnosis	Histological diagnosis
Normal ranges	♂13.5-18.0 ♀11.5-16.5	76-98	2.0-14.0	200-800	140-300	14-32 11-28	45-72	25-40		
1	5.0	88	1.2	1388	211	34	42	80	Hepatic failure Alcoholic cirrhosis Sideroblastic anaemia	Alcoholic cirrhosis (necropsy)
2	8.3	139	> 40 (on folate)	1187	—	—	—	—	Alcoholic cirrhosis	—
3	5.4	106	—	—	—	34	42	80	Carcinoma of prostate. Folate- responsive anaemia	(no necropsy)
4	10.3	112	> 40 (on folate)	2500	—	—	—	—	Alcoholism Alcoholic hepatitis	Fatty change of liver
5	7.9	104	6.0	890	—	16	42	38	Alcoholism Alcoholic hepatitis	—
6	5.1	91	—	—	—	41	40	100	Alcoholism Alcoholic hepatitis Sideroblastic anaemia	Fatty change of liver with haemosiderosis
7	10.6	97	—	—	—	—	—	—	Alcoholism	Fatty change of liver
8	9.8	105	1.2	336	—	57	54	100	Folate deficient Megaloblastic anaemia	—
9	2.5	103	0.2	425	—	45	48	93	Alcoholic cirrhosis Sideroblastic anaemia	Cirrhosis of liver
10	9.2	108	1.5	798	—	—	—	—	Sideroblastic anaemia	Haemochromatosis (necropsy)
11	11.5	108	0.7	248	80	55	54	100	Alcoholism	—
12	15.1	105	—	—	—	—	—	—	Alcoholic cirrhosis	Alcoholic cirrhosis
13	7.8	79	4.4	404	454	3	96	3	Iron deficiency anaemia. Alcohol abuse	—

iron was "locked" in the plasma cells and was unavailable to the normal storage cells and to the erythroid series. Electron micrographs of marrow plasma cells from this patient are seen in Figs. 3, 4 and 5.

The following are brief case histories of the patients:

Case 1 A 40-year-old ex-priest, who drank about one bottle of gin a day for several years, was admitted with jaundice. He had spider naevi, ascites, ankle oedema and abnormal liver function. He was anaemic with a low serum folate. Bone marrow showed megaloblastic and sideroblastic change. He developed progressive hepatic failure and died. Post-mortem examination confirmed cirrhosis.

Case 2 A 47-year-old housewife, with a known high alcohol intake, was admitted with jaundice. She had bilateral ankle oedema, spider naevi and ascites. Investigation showed high plasma bilirubin

concentrations, high SGOT and alkaline phosphatase activities, low plasma albumin and macrocytic anaemia and megaloblastic change in the marrow. The anaemia was presumed to be due to folate deficiency as it responded to folate supplements. Liver biopsy was not possible because of gross coagulation abnormality, but clinical opinion was that all the disorders were due to the alcohol problem.

Case 3 An 83-year-old patient, with known prostatic carcinoma treated with stilboestrol, was admitted with anaemia. Bone marrow showed megaloblastic change and he responded to folic acid. There was no record of alcohol abuse.

Case 4 A 63-year-old recently widowed housewife had many social and domestic problems. Her stepson stated that she was a heavy drinker. She was admitted with jaundice, sacral and ankle oedema, and hepatomegaly. Liver function studies were

Fig. 3 Case 13, Electron micrograph of marrow plasma cell. There are two organelles near the perimeter of the nucleus. One has a dense aggregate of iron. A double outer membrane is clearly visible. The other organelle is clearly a mitochondrion although internal structure is indistinct. It also contains granular, dense material which is probably ferritin. EM $\times 52\,000$

abnormal and liver biopsy showed fatty change. She had megaloblastic anaemia presumably due to folate deficiency as she responded to folate supplements, which she took of her own volition just prior to admission.

Case 5 This 55-year-old patient had been drinking heavily since his wife died and he became redundant several years previously. He was admitted because of megaloblastic anaemia. He had abnormal liver function, but liver biopsy was not performed. He responded to folate supplements, and perhaps abstinence while in hospital.

Case 6 This 55-year-old female with chronic bronchitis was admitted in an exacerbation. She was anaemic. Marrow and blood examination showed a marked defect in iron handling with sideroblastic change. She had abnormal liver function and liver biopsy showed fatty change with siderosis. Her son stated that she had been drinking for several years. She was treated with folic acid and

Fig. 4 Case 13, Electron micrograph of two adjacent plasma cells. The iron-laden organelle in the upper cell probably corresponds to a plaque on light microscopy. The iron is in granular form. EM $\times 20\,000$

advised to abstain from alcohol. A subsequent marrow aspirate showed improved iron handling.

Case 7 This 50-year-old man, with an exacerbation of chronic bronchitis, admitted to drinking 40 pints of beer a week for several years. Liver function studies were normal on admission, but subsequently became abnormal. Liver biopsy at first showed fatty change, but subsequently cirrhosis. He had normocytic, normochromic anaemia and marrow showed slight megaloblastic change.

Case 8 A 78-year-old widow with folate-deficient megaloblastic anaemia responded to folate supplements. No history of alcohol abuse was obtained and a poor diet was presumed responsible.

Case 9 A 44-year-old divorcee, who drank a bottle

Fig. 5 *Case 13, Electron micrograph of marrow plasma cell. Several iron-laden organelles adjacent to iron-free mitochondria. Traces of cristae can be made out in the upper most iron-laden organelle. The texture of the iron in the organelles suggests that it enters as ferritin and then degenerates into the more structureless haemosiderin. EM $\times 48\,000$*

of spirits a day, was admitted with confusion and had spider naevi, hepatomegaly and severe folate deficient megaloblastic anaemia. Liver biopsy showed advanced cirrhosis.

Case 10 An 82-year-old woman was admitted with oedema. She had macrocytic anaemia and low serum folate. Bone marrow showed sideroblastic change. She had abnormal liver function. Whilst in hospital she died suddenly and post-mortem examination showed haemochromatosis. There was no history of alcoholism.

Case 11 This 69-year-old bar steward in a miners' club admitted to drinking heavily for three years: five to seven vodkas and two to three pints of beer every day. His liver was markedly enlarged and liver function tests were abnormal. He had folate deficient

megaloblastic anaemia. Liver biopsy was not performed.

Case 12 A 64-year-old housewife was admitted for control of maturity-onset diabetes. Liver biopsy in 1970 showed alcoholic hepatic cirrhosis. Her GP confirmed that she had imbibed excessively in the past, but the patient claimed she had abstained for two years before the current admission. Her liver was enlarged and liver function abnormal. There was fluctuating thrombocytopenia and a grossly deranged coagulation screen, compatible with severe liver disease. She subsequently had emergency surgery for incarcerated femoral hernia and died in acute renal and hepatic failure.

Case 13 A 51-year-old unemployed labourer with a four year history of grand mal attacks was

admitted with generalised muscular pains. He was found to be anaemic with an iron deficiency picture. He admitted to drinking only three pints of beer a day. However a grand mal fit with head injury two years previously had followed a drinking bout, and there were frequent comments in his case notes about him smelling of alcohol when attending hospital. His plasma alkaline phosphatase and gamma glutamyl transpeptidase activities were raised. His anaemia was subsequently shown to be due to haematuria from a papillary bladder carcinoma.

Of the 13 patients, 10 had comments in their case notes about excessive drinking, even though the actual quantity consumed was not always recorded. The documents of the other three had no record of alcoholism.

Nine of the 10 patients who drank excessively had serious clinical problems directly related to their alcohol intake and causing death in two.

Because alcoholism is very common in the general population we compared a control group of 13 patients with the patients under study. The names of the controls were obtained as described under "Patients and Methods." The case histories were examined with particular attention to alcohol history and alcohol-related problems. Two controls only gave a history of heavy alcohol intake. None had evidence of alcoholic hepatitis, cirrhosis or other injury related to excess alcohol intake (for details see Table 3).

Discussion

The 13 patients who had iron deposits in their

marrow plasma cells did not appear to have a primary plasma cell abnormality. All had evidence of abnormal iron handling, the majority showing pathological non-ring sideroblast formation and four showing ring sideroblast formation. Eight patients had serum iron and total iron binding capacity measured and six of these showed a very high saturation of the iron-binding capacity, comparable with levels found in haemochromatosis (see Table 2). Case 13, whose transferrin saturation was only 3% and had evidence of iron-deficient erythropoiesis and significant blood loss, still retained iron in his plasma cells and probably had a normal quantity of body iron as judged by serum ferritin. These features suggest that a factor common to these patients is ineffective iron utilisation and mobilisation, and this is associated in most of the patients with megaloblastic or sideroblastic change or both. In those cases where documentation was adequate, megaloblastic change was due to folic acid deficiency; except for case 5 in whom the toxic effects of alcohol alone were possibly responsible for the change.^{7 8}

In case 6, who had frank sideroblastic change, stopping or reducing alcohol intake and taking folic acid for six weeks, led to a decrease in iron stores to normal levels, ring sideroblasts almost disappeared and plasma cell carriage of iron dropped considerably (Table 1). These findings indicated that the block to iron metabolism in her erythroid and plasma cells had simultaneously been partly relieved. The need for the erythroid cells to synthesise haemoglobin could be the reason for the greater improvement in iron handling in the erythroid cells than in the plasma cells, as seen in the second marrow.

The clinical details of the 13 patients showed that

Table 3 Controls

Control No	Age	Sex	Reason for marrow biopsy	Alcohol history	Alcohol-related problems
1	36	M	Diagnosis of folic acid and iron deficiency anaemia due to coeliac disease	2 lagers at weekend	None
2	40	F	Iron deficiency anaemia associated with menorrhagia	"Occasional"	None
3	80	M	Anaemia and high ESR. Diabetes and unresolved pneumonia	Non-drinker	None
4	65	F	Megaloblastic anaemia probably due to dietary folate deficiency. Patient immobile after cerebrovascular accident	Non-drinker	None
5	51	M	Mild folic acid deficiency associated with bronchial carcinoma	Admitted "heavy drinker"	None, other than perhaps folate deficiency
6	52	F	Iron deficiency due to carcinoma of stomach	4-5 spirits twice a week	None
7	45	M	High Hb and macrocytosis. Normoblastic marrow	10-20 pints beer a day	Macrocytosis
8	73	F	Diagnosis of pernicious anaemia	—	None
9	33	F	High platelet count high ESR. Polyarthropathy	Occasional	None
10	87	F	Diagnosis of chronic lymphatic leukaemia	—	None
11	58	F	High ESR. Disseminated carcinoma	Non-drinker	None
12	59	M	Myeloma	—	None
13	56	M	Iron deficiency and polycythaemia vera	1-2 beers a day	None

10 had documented alcohol problems. Of the remaining three, one, a female, had histological evidence of haemochromatosis at necropsy. The other two had megaloblastic anaemia responsive to folic acid. These conditions are often associated with alcohol excess, and it is possible (though not proved) that these three also were covert drinkers. In the 10 established drinkers, the alcohol problem contributed to the cause of death in two of the patients and appeared unusually severe in all.

The association of alcohol abuse and iron-carrying plasma cells does not necessarily imply a causal relation. The first problem is common, the second is rare. However a fortuitous association between the two conditions is unlikely in view of the absence of serious alcohol-related problems in a matched control group.

We must now consider what is the subcellular localisation of the iron in the plasma cell. Other work on electron microscopy of these cells (see introduction) has never defined the organelle which contains the iron granules. We believe that the granules are in mitochondria, for the following reasons:

(i) Electron microscopy of normal plasma cells shows many well developed mitochondria between strands of rough endoplasmic reticulum, generally near the nucleus. The iron-containing vacuoles in our studies (Figs. 3, 4, 5) and in those of other workers (see introduction) are similar in size, shape, and position in the cell to normal mitochondria. Finer details of structure are largely obscured by the electron-dense iron in the vacuoles but a double outer membrane can be seen in Figs. 3, 4, 5, similar to that in adjacent normal mitochondria. Traces of cristae can also be made out in the iron-loaded organelles in Figs. 3 and 4.

The damage sustained by iron loaded mitochondria in ring sideroblasts has been clearly shown by the work of Goodman and Hall.⁹ Their electron micrographs showed, in either chloramphenicol-induced or porphyria cutanea tarda-associated ring sideroblasts, that whereas some mitochondria are completely iron-free, others immediately adjacent might have a very heavy load of iron. Some organelles containing iron "appear to be mitochondria with cristae distorted and disruption of the usual mitochondrial architecture." In some mitochondria, finely dispersed iron was seen, whereas in others a dense deposit completely obscured the organelle's features. These features are remarkably similar to those of the iron-containing organelles in the plasma cells of this study.

(ii) Studies by a number of workers on animal models, reviewed by Romslo¹⁰ showed that mitochondria of reticulocytes have the function of

accumulating iron by an energy-dependent mechanism as it is delivered to the cell by transferrin, and hold a key position in the metabolism of that iron. Moreover Romslo showed that this function is not limited to the mitochondria of erythroid cells, but that mitochondria of other tissues such as kidney, heart, and spleen have a qualitatively similar mechanism for iron accumulation. As expected, the quantity of iron taken up by reticulocyte mitochondria was assessed as several times greater than that taken up by liver mitochondria, because of the specialised function of haemoglobin synthesis in reticulocytes. Mitochondria of all tissues require iron for the enzymes of the respiratory chain particularly the cytochromes. It seems likely that the function of iron accumulation is designed to supply the iron requirements for these enzymes, and that it is common to all mitochondria-containing cells. Any abnormal accumulation of iron in a cell would therefore be most likely to occur in or near the mitochondria.

Why does an excessive accumulation of iron take place in the mitochondria of alcoholic patients' marrow plasma cells? Iron handling is known to be disturbed in alcoholism. Alcoholics tend to have a higher than normal serum iron^{11 12} and saturation of iron-binding capacity.^{13 14} They have increased iron absorption and tend to develop iron overload when they become folic acid-deficient (which they are particularly prone to do).¹⁴⁻¹⁷ Alcoholism is also a common cause of sideroblastic anaemia, which is reversible on withdrawal of alcohol,^{14 18 19} even in a matter of days.¹³ We believe that iron in plasma cells may be acquired in alcoholic patients by a mechanism which is qualitatively similar to that observed in ring sideroblasts in alcohol-induced sideroblastic disease.

The ring sideroblast in sideroblastic anaemia of whatever cause is a normoblast with granules of iron in a ring or collar round the nucleus. The iron granules have been shown by electron microscopy to be situated in damaged mitochondria^{9 17 20} as mentioned above. Dynamically, although there is increased marrow iron uptake in sideroblastic anaemias, there is defective utilisation of iron.²¹ The biochemical lesion in sideroblastic anaemias is thought to be defective haem synthesis²² and one cause of this is diminished availability of pyridoxal-5-phosphate.²¹ Alcoholic patients have impairment of haem synthesis and pyridoxine metabolism^{12 14} which has been shown to be associated with hyperferraeemia, increased plasma iron turnover, ineffective erythropoiesis, and sideroblastic anaemia.¹² Alcoholics often have reduced pyridoxine intake, show impaired phosphorylation of pyridoxine to active pyridoxal-5-phosphate with reduced plasma levels and accelerated hydrolysis of pyridoxal-5-

phosphate.^{12 14 23} Pyridoxal phosphate normally catalyses two steps in haem synthesis which are inhibited by alcohol and which take place within the mitochondrion (steps 1 and 6 in Fig. 6). Ferrochelatase activity is reduced by alcohol²⁴ which also affects step 6 (see Fig. 6). Thus in sideroblasts, iron, failing to be incorporated into haem, accumulates as haemosiderin within or associated with the mitochondria.

This is not, however, the complete story. Ponka and Neuwirt²⁵ showed that in normal erythroid precursors the amount of iron entering the cell from transferrin was inversely controlled by the haem concentration inside that cell. Thus an accumulation of haem inhibits iron entry, whereas inadequate haem formation leads to increased iron entry. These workers opined that the accumulation of iron in ring sideroblasts is due not only to inadequate incorporation of iron into haem but is also the result of an absolute increase of iron entry into erythroblasts.

We now postulate that these two factors, ineffective utilisation of iron and excessive deposition of iron, may be operating in other cells besides erythroblasts, including plasma cells. Although the manufacture of haem is quantitatively most important in haemoglobin-synthesising cells (erythroblasts and reticulocytes), it is a pathway common to all mitochondria-containing cells, as haem is required for the haem-containing enzymes of the respiratory chain; chiefly the cytochromes. The haem groups of cytochromes are believed to be derived from

protoporphyrin IX by the same biochemical pathway as the haem group of haemoglobin.²⁶ Cytochrome synthesis would therefore be expected to be subject to the same biochemical inhibitory agents as haemoglobin, such as alcohol.

The work of Romslo¹⁰ and Flatmark and Romslo,²⁷ showing that iron accumulation is a function of mitochondria of all tissues and closely linked with the activity of the respiratory chain (in which cytochromes are involved), suggests that the control of iron uptake in non-erythroid cells may well be controlled by haem, in exactly the same way as in erythroid precursors.²⁵ An agent, such as alcohol, which inhibits haem formation could cause increased uptake of iron from transferrin in all respiring cells, in the same way as in erythroblasts. This hypothesis would also account for the excess iron found in hepatocytes and other tissues in alcoholics.

It therefore seems quite possible that the haemosiderin granules in the marrow plasma cells of our patients are analogous to haemosiderin granules in ring sideroblasts, by a process of ineffective utilisation and excessive accumulation.

Further support for the hypothesis comes from the fact that four of the 13 patients described had associated ring sideroblasts in their marrows. The known reversibility of sideroblastic change on stopping alcohol may account for the failure to find ring sideroblasts in the other patients. Plasma cells which have accumulated iron would presumably be less able to metabolise this, on removal of the

Fig. 6 Biosynthesis of Haem

inhibiting effects of alcohol, than erythroblasts; because the latter need to synthesise larger quantities of haem.

The hypothesis does not explain the presence of iron in only a certain percentage of plasma cells, or indeed why in some plasma cells certain mitochondria are heavily laden whilst others are spared. This latter feature is noted also in ring sideroblasts.⁹ In any cell there may be a differential function amongst mitochondria so that at one time certain mitochondria may be resting and therefore not using iron, whilst others are actively metabolising and needing to replenish their respiratory enzymes. Again, available iron is likely to be diverted particularly to those plasma cells which are required to produce antibody. Thus, a severe infection and a sudden requirement for antibody production may stress a certain population of plasma cells and cause worsening of an already faulty mechanism for iron handling. The excess iron must also interfere with the function of the cells and may account for the well-recognised liability of the alcoholic patient to severe infections.

Lastly, when alcoholism is such a common problem, why should iron-carrying plasma cells be so rarely seen? The answer to this may lie in the pattern of drinking habits. Alcohol-induced sideroblastic change reverses in a few days after stopping drinking.¹³ The level of ferrochelatase activity rises with the fall in blood alcohol level after suppression by alcohol.²⁴ It is possible that iron can only accumulate in large quantities in those patients who drink constantly and without remission, so that no time is allowed for the suppressive effects to reverse.

Conclusion

The presence of iron in marrow plasma cells is an unusual finding, which appears to be associated with unusually severe chronic alcohol problems, and which should be sought in routine marrow examinations, especially those showing megaloblastic or sideroblastic change. The biochemical events leading to iron deposition in plasma cells is probably a pathological process analogous to the formation of ring sideroblasts.

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References

- Koszewski BJ. The occurrence of megaloblastic erythropoiesis in patients with haemochromatosis. *Blood* 1952;7:1182.
- Goodman JR, Hall SG. Plasma cells containing iron. An electron micrograph study. *Blood* 1966;28, 1:83.
- Lerner RG, Parker JW. Dysglobulinaemia and iron in plasma cells. *Arch Intern Med* 1968;121:284.
- De Lellis RA. Iron containing plasma cells in a healed recluse spider bite. *Arch Pathol* 1971;92:254.
- Karcioglu GL, Hardison JE. Iron containing plasma cells. *Arch Intern Med* 1978;138:97.
- Shanmugathasa M, Sobel HJ, Marquet E. Plasma cells with inclusions containing iron. *Arch Pathol Lab Med* 1979;103:577.
- Eichner ER, Hillman RS. Effect of alcohol on serum folate level. *J Clin Invest* 1973;52:584.
- Wu A, Chanarin I, Slavin G, Levi AJ. Folate deficiency in the alcoholic, its relationship to clinical and haematological abnormalities, liver disease and folate stores. *Br J Haematol* 1975;29:469.
- Goodman JR, Hall SG. Accumulation of iron in mitochondria of erythroblasts. *Br J Haematol* 1967;13:335.
- Romslo I. Energy-dependent accumulation of iron by isolated rabbit reticulocyte mitochondria. *Biochim Biophys Acta* 1974;357:34.
- Houriham DO'B, Weir DG. Suppression of erythropoiesis by alcohol. *Br Med J* 1970;ii:86.
- Hines JD, Cowan DH. Studies on the pathogenesis of alcohol-induced sideroblastic bone-marrow abnormalities. *N Engl J Med* 1970;283:441.
- Hines JD. Reversible megaloblastic and sideroblastic marrow abnormalities in alcoholic patients. *Br J Haematol* 1969;16:87.
- Colman N, Herbert V. Haematological complications of alcoholism: overview. *Semin Hematol* 1980;17, 3:164.
- Cowan DH, Hines JD. Thrombocytopenia of severe alcoholism. *Ann Intern Med* 1971;74:37.
- Celada A, Rudolf H, Donath A. Effect of experimental chronic alcohol ingestion and folic acid deficiency on iron absorption. *Blood* 1979;54, 4:906.
- Bessis MC, Jensen WN. Sideroblastic anaemia, mitochondria and erythroblastic iron. *Br J Haematol* 1965;11:49.
- Hines JD, Grasso JA. The sideroblastic anaemias. *Semin Hematol* 1970;7:86.
- Eichner ER, Hillman RS. The evolution of anaemia in alcoholic patients. *Am J Med* 1971;50:218.
- Grasso JA, Hines JD. Comparative electron microscopic studies of refractory and alcoholic sideroblastic anaemia. *Br J Haematol* 1969;17:35.
- Bottomley SS. Porphyrin and iron metabolism in sideroblastic anaemia. *Semin Hematol* 1977;14, 2:169.
- Bateman CJT, Mollin DL. Sideroblastic anaemia. *Br J Hosp Med* 1970;Sept:371.
- Lumeng L, Li T. Vitamin B₆ metabolism in chronic alcohol abuse. *J Clin Invest* 1974;53:693.
- Moore MR. The effects of ethanol on heme biosynthesis. In: Thurman RG, ed. *International Symposium of Alcohol and Aldehyde Metabolizing Systems*. New York: Academic Press, 1974;1:543.
- Ponka P, Neuwirt J. Haem synthesis and iron uptake by reticulocytes. *Br J Haematol* 1974;28:1.
- Gidari AS, Levere RD. Enzymatic formation and cellular regulation of heme synthesis. *Semin Hematol* 1977;14, 2:145.
- Flatmark T, Romslo I. Energy-dependent accumulation of iron by isolated rat liver mitochondria. *J Biol Chem* 1975;250, 16:6433.