action by manufacturers and retailers. In the case of fireguards and oil heaters this was stimulated by Government intervention. Up to the present the action on nightdresses has been voluntary but now has legal backing. Underlying all these developments has been the work on standardization, for which credit is particularly due to the British Standards Institution and the Fire Research Station. Consumer organizations have also helped in producing an informed public demand for safer products.

Another example of successful control by manufacturers was the substitution in 1957 of the explosive "thunder flash" type of firework by a less dangerous "banger." This resulted in reduction by two-thirds of the injuries due to these fireworks being (wrongly) held in the hand (Jackson, 1961). However, it is hard to see how the majority of firework accidents can be prevented unless explosives are kept entirely out of the hands of children and high-spirited teenagers.

In the light of the modest successes already achieved it should be possible to tackle the remaining problems. These include the more thorough guarding of open fires, provision of safe nightwear for the elderly and infirm, and safer daywear, particularly for girls and women, though the relative immunity of males has been reduced with the introduction of unproofed cottons and celluloses for trousers. New hazards also may increase in importance—for instance, accidents with flammable liquids are becoming more frequent, as also are deaths from conflagration. These present new challenges to research into details of causes and prevention.

Summary

Since the previous survey eight years ago both annual deaths from burns and admissions to the Burns Unit have increased. The main increases have been among persons aged 15 to 65 years.

Just under half the cases in Birmingham were due to direct or indirect contact with domestic heating appliances. The unguarded open coal-fire was responsible for almost half of the accidents due to these causes and half of the deaths.

Accidents due to unguarded electric fires have shown a dramatic fall from 24% to 4% in the present study. There is also a downward trend in the national mortality figures due to this cause.

Ignition of flammable liquid causes an increasing number of injuries to schoolboys and men.

Accidents where clothing caught fire caused 90% of the deaths, but there has been a change in emphasis in the present Birmingham series. The accidents due to children's nightdresses catching fire have fallen by half and are outnumbered by those due to the ignition of dresses. Accidents involving clothing of females aged 15–64 are now more common. There has also been an increase in accidents in which trousers caught fire.

Cotton fabrics were involved in four-fifths of accidents where clothes caught fire.

Preventive action has had success in improved guarding of gas and electric fires, elimination of the more dangerous oil burners, and encouragement of safer nightwear for children.

Further action is recommended for improved guarding of open fires and the wider use of safe fabrics for both day and night wear.

References

Birmingham Consumer, 1964, **4**, 29.
Colebrook, L., and Colebrook, V. (1949). *Lancet*, **2**, 181.
—— —— Bull, J. P., and Jackson, D. M. (1956). *Brit. med. J.*, **1**, 1379.
Fire Research, 1960, p. 36. H.M.S.O.
Jackson, D. M. (1953). *Ann. roy. Coll. Surg. Engl.*, **13**, 236.
—— (1961). *Brit. med. J.*, **2**, 1184.
Lawson, D. I. (1964). *Quart. Instn Fire Engrs*, **24** (53), 73.
Maisels, D. O., and Corps, B. V. M. (1964). *Lancet*, **1**, 1298.
Registrar-General's Statistical Review of England and Wales, Part 1, Tables, Medical, for years 1955–62.
Tempest, M. N. (1956). *Brit. med. J.*, **1**, 1387.

Effect of Alcohol on Iron Absorption

R. W. CHARLTON,* M.D., B.SC., M.R.C.P.ED.; P. JACOBS,* M.B.; H. SEFTEL,† M.B., B.SC., DIP.MED.
T. H. BOTHWELL,* M.D., M.R.C.P.

Brit. med. J., 1964, 2, 1427–1429

There are several observations which suggest a relation between excessive consumption of alcohol and the development of iron overload. For example, approximately a third of the patients exhibiting the full-blown clinical manifestations of idiopathic haemochromatosis have a significant alcoholic background (Sheldon, 1935; Finch and Finch, 1955). Furthermore, there is evidence that alcoholics as a group tend to have iron stores that are greater than normal (Herbut and Tamaki, 1946; MacDonald and Mallory, 1960). Finally, there is suggestive evidence that the severity of the tissue siderosis so commonly noted in the adult Bantu males of South Africa is closely related to the drinking habits of these subjects (Seftel *et al.*, 1961).

There are several possible reasons for these various associations. In the first place, analyses of the home-brewed alcoholic beverages consumed by the Bantu have revealed high iron concentrations (Walker and Arvidsson, 1953), and it has been calculated that many males ingest between 50 and 100 mg. of iron daily from this source alone (Bothwell *et al.*, 1964). A similar, though less striking, association between iron and alcoholic intakes has recently been pointed out by MacDonald (1963), who has shown that most European and United States wines contain significant amounts of iron. (For example, the average iron concentration in French wines is 8.8 mg./l., and in United States wines 4.9 mg./l.). A second possible way in which excessive consumption of alcohol may lead to iron overload is through its pathological sequelae, such as chronic pancreatitis and chronic liver disease. Deficiency of the exocrine secretions of the pancreas has been shown to be associated with increased absorption of iron from the gut (Taylor *et al.*, 1931; Davis and Badenoch, 1962), and there is recent evidence indicating that some subjects with cirrhosis of the liver absorb iron excessively (Conrad *et al.*, 1962; Callender and Malpas, 1963).

* Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa.
† Baragwanath Hospital, Johannesburg, South Africa.

There are therefore several possible reasons why so many heavy drinkers have increased iron stores. However, one possibility has not been investigated—namely, that alcohol itself directly enhances iron absorption. The present investigation was carried out to try to answer this point.

Material and Methods

The absorption of 5 mg. of iron was assessed in 31 haematologically normal subjects and in four patients with histamine-fast achlorhydria. Because of the well-known variability in iron absorption from subject to subject, a double isotope technique was used in which each individual served as his own control. (The validity of this approach has been demonstrated in a previous communication (Jacobs *et al.*, 1964).) The iron was administered in the fasting state. On one day it was dissolved in 250 ml. of water, and on the following day in 60 ml. of whisky or brandy, made up to a final volume of 250 ml. with water. In half the experiments the order of administration was reversed. Isotope labelling was with 70 μc of ^{55}Fe on the one occasion and with 5 μc of ^{59}Fe on the other. In different experiments the iron was administered as ferric chloride, as ferrous ascorbate (with 50 mg. of ascorbic acid), and as rat haemoglobin. Duplicate blood samples collected two weeks later were digested, electroplated on to copper disks, and differentially counted for the two isotopes as described previously (Bothwell and Finch, 1962). The relative percentage absorptions of the two doses were then calculated on the assumption that 80% of the iron absorbed from the gut was present in the red-cell mass at two weeks, and that the blood volume was 70 ml./kg. Results were therefore corrected by a factor of 10/8.

Results

The absorption of iron given as ferrous ascorbate was assessed in six normal subjects. The mean absorption was 18.8% in water and 17.5% in alcohol (see Table). There was also no enhancement of the absorption of haemoglobin iron in the presence of alcohol, the mean figures in eight subjects being 14.9% in water and 13.4% in alcohol. In contrast, alcohol caused a marked increase in the absorption of iron given as ferric chloride. In 17 subjects the mean absorption in alcohol was 22.6%, as compared with 4.1% in water (see Chart). This effect could not, however, be demonstrated in four subjects with histamine-fast achlorhydria (a mean of 3.5% in water and 5.2% in alcohol).

Effect of Alcohol on the Absorption of 5 mg. of Iron Given as (A) Ferrous Ascorbate and (B) Haemoglobin

	Ferrous Ascorbate		Haemoglobin	
	Without Alcohol	With Alcohol	Without Alcohol	With Alcohol
Percentage absorption	8·3	4·6	12·8	9·7
	21·7	14·5	6·1	8·2
	20·5	16·1	11·4	14·1
	22·5	28·3	10·6	8·4
	20·2	14·7	21·6	15·3
	19·5	27·0	19·0	18·6
			20·5	8·9
			17·1	23·6
Mean	18·8	17·5	14·9	13·4

Discussion

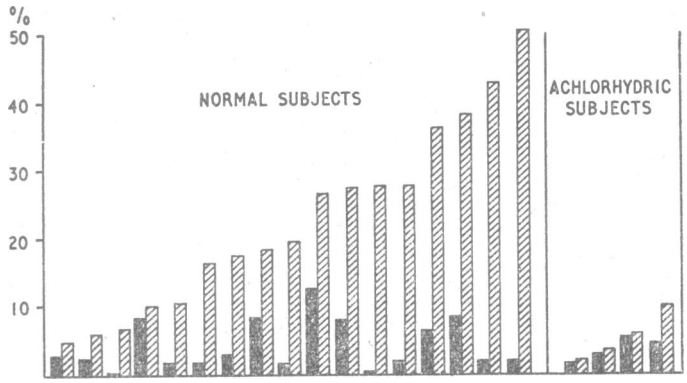
In a previous investigation the effect of hydrochloric acid on iron absorption was studied in subjects with histamine-fast achlorhydria (Jacobs *et al.*, 1964). Hydrochloric acid was found to enhance markedly the absorption of ferric iron and to cause a modest increase in the absorption of ferrous iron. In contrast, haemoglobin iron absorption was not increased by acid. Although the reasons for these differences were not established, it seems likely that hydrochloric acid acts by maintaining ferric iron in solution until it reaches the absorbing area of the duodenum. The relatively small effect observed with ferrous iron is compatible with this thesis, since it is known that ferrous ions remain in solution at a much higher *p*H than do ferric ions (Hodgman *et al.*, 1958). The fact that the absorption of haemoglobin iron is not increased by acid adds further weight to evidence obtained by other workers which suggests that this organic iron complex is absorbed in a manner different from simple iron salts (Turnbull *et al.*, 1962).

In the present study alcohol was found to potentiate the absorption of ferric iron considerably, but to have no effect on the absorption of ferrous or haemoglobin iron. The similarity between these results and those obtained previously with hydrochloric acid suggested that alcohol might be exerting its effect by stimulating the production of gastric acid. The fact that the administration of alcohol did not increase the absorption of iron in four subjects with histamine-fast achlorhydria would be compatible with this hypothesis.

Whether the present findings bear any relation to the pathogenesis of iron overload is still not clear. While it is known that excessive amounts of iron are present in the fermented beverages consumed by the Bantu (Walker and Arvidsson, 1953), it has not been possible to show an enhancement of absorption when iron has been administered in Bantu beer (Bothwell *et al.*, 1964). However, it should be noted that the type of beer which was tested had a very low alcohol content (±3%), and it remains possible that the more potent adulterated drinks consumed by many of these subjects may enhance iron absorption significantly.

Recent evidence suggests that the present findings may have a wider relevance. It has been pointed out that many wines from different parts of the world contain significant amounts of iron, and it has been suggested that the high incidence of iron overload in alcoholic subjects is a result of the excessive iron intake (MacDonald, 1963). It should, however, be noted that wines contain 10–20% alcohol, and the absorption of iron taken in this way may thus be enhanced.

These considerations do not exclude the possibility that other factors may contribute to the association between iron overload and the excessive consumption of alcohol. Pancreatitis is common in alcoholics, and there is now good evidence that deficiency of the exocrine secretions of the pancreas is associated with excessive absorption of iron. This has been shown in animals after pancreatectomy (Taylor *et al.*, 1931), ligation of the pancreatic duct (Taylor *et al.*, 1935 ; Gillman *et al.*, 1947 ; Kinney *et al.*, 1950), and ethionine-induced pancreatic damage (Kinney *et al.*, 1955), and in patients with chronic pancreatitis



Effect of alcohol on the absorption of 5 mg. of iron given as ferric chloride. Each pair of columns represents absorption with alcohol (hatched) and without alcohol (black) in the same individual. In normal subjects mean absorptions were 4.1% with water and 22.6% with alcohol, while in achlorhydric subjects the corresponding figures were 3.5% and 5.2%.

(Davis and Badenoch, 1962). Furthermore, there is evidence that the increased absorption can be reduced by the giving of pancreatic extract (Kinney *et al.*, 1950 ; Davis and Badenoch, 1962 ; Saunders *et al.*, 1963). The fact that cirrhosis is common in alcoholics may also be of relevance, since it has been shown that some cirrhotic subjects absorb excessive amounts of iron even when the body stores are normal or increased (Conrad *et al.*, 1962). It is, however, still not clear whether these effects are secondary to the cirrhosis itself or to associated pancreatic damage (Callender and Malpas, 1963). Lastly, alcoholics as a group eat suboptimal diets, and there are several experimental studies showing increased absorption of iron when the diet is low in certain nutrients but high in iron. These diets have included low phosphate (Hegsted *et al.*, 1949), low protein, high fat (Kaufman *et al.*, 1958), and choline-deficient (MacDonald, 1960) regimes.

With all these factors contributing to the excessive absorption of iron it is not surprising that doubt has been cast on whether idiopathic haemochromatosis occurs as a distinct entity. The arguments against its existence have been presented by MacDonald (1961, 1963), who believes the condition to be a variant of alcoholic cirrhosis occurring in subjects exposed to a high iron diet. Some support for this suggestion is provided by the fact that many patients presenting with the disease have a background of alcoholism (Sheldon, 1935 ; Finch and Finch, 1955). There is, however, a strong body of evidence, accumulated from many sources, which indicates the existence of a specific metabolic disorder in which excessive amounts of iron are absorbed from a *normal* diet.

Firstly, it should be emphasized that a large number of reported patients with the disease have not been alcoholic, and no other source of excessive dietary iron has been uncovered in these cases. Secondly, there are several family studies in which varying degrees of iron overload have been demonstrated in relatives of patients with haemochromatosis, thus supporting the concept of an inherited metabolic disorder (Bothwell *et al.*, 1959 ; Williams *et al.*, 1962). The fact that only a proportion of siblings living in the same household have shown increased stores can also be taken as evidence against the idea that some environmental factor, such as a high dietary intake, is essential in pathogenesis. Thirdly, it has been possible to show an abnormally high absorption of radioiron in some patients with the fully developed disease (Alper *et al.*, 1951 ; Bothwell *et al.*, 1953). This is especially so in young subjects, and the failure to demonstrate increased absorption in some older patients may well be due to the inhibitory effect exerted by the enormous iron stores. Support for this contention has been provided by the finding of very high absorption rates in such individuals after reduction of stores by repeated phlebotomy. This has been noted at a time when the haemoglobin level was normal and the serum iron normal or even raised (Pirzio-Biroli *et al.*, 1958).

Although consideration of these various findings suggests the existence of a specific metabolic disorder resulting in excessive iron absorption, it is probable that only a proportion of affected individuals develop the clinical manifestations of haemochromatosis. The size of the accumulated iron deposits in any particular case must depend upon a number of factors. These include the degree to which the absorptive rate deviates from the normal, the amount of iron in the diet, the duration of the period of increased absorption, and the quantity of iron lost from the body. On this basis the excessive intake of iron, particularly when present in alcohol, might be expected to accelerate the development of the full clinical syndrome in subjects who would otherwise have remained asymptomatic.

Summary

Alcohol in the form of whisky or brandy markedly increased the absorption of ferric chloride in normal subjects, but had no effect upon the absorption of ferrous ascorbate or haemoglobin iron. Some evidence was obtained to suggest that this action was due to the stimulation of hydrochloric acid production in the stomach.

These findings may have some relevance to the well-established association between excessive consumption of alcohol and the development of iron overload.

This study was supported in part by a grant (AM 04912-03) from the National Institutes of Health, U.S.A., and in part by grants from the Council for Scientific and Industrial Research and the Atomic Energy Board, South Africa.

References

Alper, T., Savage, D. V., and Bothwell, T. H. (1951). *J. Lab. clin. Med.*, **37**, 665.
Bothwell, T. H., Cohen, I., Abrahams, O. L., and Perold, S. M. (1959). *Amer. J. Med.*, **27**, 730.
—— van Doorn-Wittkampf, H. van W., Du Preez, M. L., and Alper, T. (1953). *J. Lab. clin. Med.*, **41**, 836.
—— and Finch, C. A. (1962). *Iron Metabolism*, p. 32. Little, Brown, Boston.
—— Seftel, H., Jacobs, P., Torrance, J. D., and Baumslag, N. (1964). *Amer. J. clin. Nutr.*, **14**, 47.
Callender, S. T., and Malpas, J. S. (1963). *Brit. med. J.*, **2**, 1516.
Conrad, M. E., Berman, A., and Crosby, W. H. (1962). *Gastroenterology*, **43**, 385.
Davis, A. E., and Badenoch, J. (1962). *Lancet*, **2**, 6.
Finch, S. C., and Finch, C. A. (1955). *Medicine (Baltimore)*, **34**, 381.
Gillman, J., Gillman, T., Mandelstam, J., and Gilbert, C. (1947). *Nature (Lond.)*, **159**, 875.
Hegsted, D. M., Finch, C. A., and Kinney, T. D. (1949). *J. exp. Med.*, **90**, 147.
Herbut, P. A., and Tamaki, H. T. (1946). *Amer. J. clin. Path.*, **16**, 640.
Hodgman, C. D., Weast, R. C., and Selby, S. M. (1958). *Handbook of Chemistry and Physics*, p. 1740. Chemical Rubber Publishing Co., Cleveland, Ohio.
Jacobs, P., Bothwell, T. H., and Charlton, R. W. (1964). *J. appl. Physiol.*, **19**, 187.
Kaufman, N., Klavins, J. V., and Kinney, T. D. (1958). *Lab. Invest.*, **7**, 369.
Kinney, T. D., Finch, C. A., Kaufman, N., Hegsted, M., and Partington, P. F. (1950). *Amer. J. Path.*, **26**, 746.
—— Kaufman, N., and Klavins, J. (1955). *J. exp. Med.*, **102**, 151.
MacDonald, R. A. (1960). *Amer. J. Path.*, **36**, 499.
—— (1961). *Arch. intern. Med.*, **107**, 606.
—— (1963). Ibid., **112**, 184.
—— and Mallory, G. K. (1960). Ibid., **105**, 686.
Pirzio-Biroli, G., Bothwell, T. H., and Finch, C. A. (1958). *J. Lab. clin. Med.*, **51**, 37.
Saunders, S. J., Bank, S., Airth, E., and Williams, J. (1963). *S. Afr. med. J.*, **37**, 1106.
Seftel, H. C., Keeley, K. J., Isaacson, C., and Bothwell, T. H. (1961). *J. Lab. clin. Med.*, **58**, 837.
Sheldon, J. H. (1935). *Haemochromatosis*, p. 274. Oxford University Press, London.
Taylor, J., Stiven, D., and Reid, E. W. (1931). *J. Path. Bact.*, **34**, 793.
—— —— —— (1935). Ibid., **41**, 397.
Turnbull, A., Cleton, F., and Finch, C. A. (1962). *J. clin. Invest.*, **41**, 1897.
Walker, A. R. P., and Arvidsson, U. B. (1953). *Trans. roy. Soc. trop. Med. Hyg.*, **47**, 536.
Williams, R., Scheuer, P. J., and Sherlock, S. (1962). *Quart. J. Med.*, **31**, 249.