POISONING WITH A PREPARATION OF IRON, COPPER, AND MANGANESE

BY

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Most iron salts are relatively inert, and modern therapeutic practice recommends their use in full doses. Certain iron preparations are, however, apt to cause dyspepsia, and even one Blaud's pill may occasion abdominal discomfort in susceptible individuals. According to Goodman and Gilman (1943) iron salts used in the treatment of anaemias may cause " gastric distress, colicky pain, and diarrhoea. These complaints are more prominent after ferric salts than after ferrous salts, and more common with the soluble than the insoluble preparations." They consider that this is especially true of ferrous sulphate, owing, in part at least, to the smaller doses used.

Cases of poisoning due to the ingestion of iron are extremely rare. Smith and Cook (1934) mention a case of a girl who swallowed 1 oz. (28 g.) of ferrous sulphate and recovered. Nearly all the cases of poisoning by iron preparations are due to the tincture of perchloride of iron, but a case of iron encephalopathy has been reported by Hurst (1931) following the oral administration of huge doses of iron and ammonium citrate. He states that no other example of remote symptoms due to iron (other than local gastro-intestinal effects) has been reported.

Some experimental work has been done on iron poisoning, but for the most part the method of administration has been by injection. McGuigan (1926) quotes Kunkel to the effect that the fatal intravenous dose of iron for dogs is from 20 to 50 mg. per kg. of body weight. Meyer and Williams, according to McGuigan (1926), found that 0.6 g. of ferrous sulphate injected into the veins of a dog caused pronounced vomiting and diarrhoea ; 8 g. given orally proved fatal to a dog in 26 hours, and the necropsy showed ecchymosis of the stomach and intestines. McGuigan also reports the death of a man following the ingestion of 45 ml. of tincture of iron.

Copper sulphate falls into the category of irritant metallic poisons. Acute poisoning with this substance is very rare, and fatal cases are still more uncommon. Consequently the fatal dose of this salt is unknown, but Smith and Cook (1934) advance the suggestion that doses of 1/2 oz. (14 g.) and upwards would act as powerful irritants on adults, and that a much smaller quantity would suffice to destroy infants or children. Copper sulphate is a powerful emetic, and may be used clinically for this purpose in doses of from 5 to 10 gr. (0.32 to 0.65 g.). If taken in larger quantities it causes acute gastro-enteritis. Because of its irritant properties, if this salt is given as an emetic and fails to act the stomach must be promptly emptied by some other means (Douthwaite, 1931). Retained copper is absorbed from the intestine and passes to the liver, where it is stored. It is excreted partly in the bile and partly in the urine.

The irritant properties of copper sulphate are to some extent an asset. On ingestion vomiting occurs promptly and diarrhoea follows later. These processes aid in eliminating the poison from the system, so preventing absorption and reducing the risk of remote toxic effects on other organs. It has been observed (Smith and Cook, 1934) that in non-fatal cases jaundice is sometimes a symptom, and this indicates that copper salts are apt to lead to liver damage. A considerable volume of experimental work has been done on this problem in the form of animal feeding experiments. Mallory, Parker, and Nye (1921) announced that it was possible to produce pigmentation and cirrhosis of the liver in rabbits and sheep by the oral administration of copper salts or of metallic copper in powdered form. Their results have been confirmed by Hall and Butt (1928), and denied by Flinn and Von Glahn (1929) and by Polson (1929), who claim that copper does not produce either pigmentation or cirrhosis, and that the pigmentation seen by Mallory and his co-workers is a natural phenomenon in the rabbit and is due to diet only. More recently Mallory and Parker (1931) have repeated their experiments and have found that copper given by injection in sufficient doses will kill a rabbit in from 24 hours to two to three weeks, and that necrosis and pigmentation of the liver cells can be demonstrated histologically. They assert that by special staining methods they have succeeded in demonstrating the copper in the liver cells. If the rabbits survive for a variable period, cirrhosis of the liver follows. They also describe the occurrence of necrosis of the tubular epithelium of the kidneys. Their results are supported by Hall and MacKay (1931), who found that 50% of their copper-fed rabbits developed cirrhosis of the liver, and that large quantities of copper were stored in this organ. Indirect support is also given by the finding of Gordon and Rabinowitch (1933) that in cirrhosis of the liver in man the copper content is increased. Thus there seems to be some evidence that copper salts can produce liver damage in addition to the gastro-intestinal irritation admitted by all toxicologists.

Manganese is generally regarded as being a relatively non-toxic element. A search of the literature has failed to reveal a case of acute manganese poisoning in man. There are, however, reports of chronic poisoning of industrial origin where the symptoms are those of hepatolenticular degeneration. The neurological syndrome resembles in some respects that characteristic of Parkinson's disease (Goodman and Gilman, 1943). Von Oettingen (1935) reports that the lesions of the liver and central nervous system seen clinically can be produced in animals with toxic amounts of manganese, while Hurst and Hurst (1928) failed to detect any changes in the brain even in

the presence of gross damage to the liver. A single large dose of a manganese salt given subcutaneously will prove fatal in one to two days, while smaller doses repeated will produce cirrhotic changes in weeks or months ; similar changes are found in rats which have had manganous chloride added to the diet (Findlay, 1924). Hurst and Hurst (1928) also produced acute and chronic changes after giving injections of manganese. It is fairly clear that both acute and chronic damage closely allied to acute yellow atrophy and cirrhosis, as seen in man, can be produced in animals experimentally.

It is questionable whether these experiments have proved the toxicity of manganese under ordinary conditions in man. According to Richards (1930) the bulk of the evidence seems to show that when ingested, even in fairly large amounts, manganese compounds have no toxic effects. He quotes the work of Reiman and Minot (1920) and of von Oettingen and Sollman to prove that feeding manganese ores to dogs and pigeons over a long period and in large amounts fails to produce any significant changes in the manganese content of the blood and tissues or any pathological symptoms. Richards fed manganese to pigs and found no toxic symptoms after the daily ingestion of 3.5 g. of manganese citrate for nearly nine months.

Case 1

A healthy boy aged 3 years 3 months took a box of tablets off the kitchen table in his home at 12 noon on April 23, 1946. According to the mother's estimate the box contained about 50 tablets. At 12.30 p.m. the same day the box was found to be empty, and the child admitted having swallowed all the tablets. Each tablet contained ferrous sulphate exsic. 3 gr. (0.2 g.), copper sulphate 1/25 gr. (2.6 mg.), and manganese sulphate 1/25 gr. Shortly afterwards the boy vomited and a few tablets were returned. During the afternoon of that day the child slept fitfully, was thirsty, and appeared to be very weak. At 6 p.m. he vomited again, and the vomitus was clear fluid only. He had a fairly comfortable night, and next morning his general condition had improved. On the following day he showed no symptoms likely to cause alarm till 10 a.m., when his skin became yellow, his pupils dilated, and he was very restless. The child's condition steadily deteriorated till 5.30 p.m. on April 25, when he died—53 hours after taking the tablets. Medical advice was sought by the boy's mother immediately she discovered what he had done, but no treatment was considered necessary in view of the fact that he had vomited. Actually he was not seen by a doctor till 48 hours afterwards and he had no treatment during the illness.

Post-mortem Examination.—The only significant external findings were a suggestion of jaundice in the sclerotics and some abdominal distension. The stomach contained 3 oz. (75 g.) of dark coffee-ground material and the mucous membrane along the lesser curvature was brown and necrotic. The remainder of the mucosa was rather oedematous but not acutely inflamed. The anterior wall of the stomach was stained blue and the subperitoneal vessels were injected. The small bowel was filled with black semi-solid material which had stained the rather oedematous mucous membrane, and there was vascular engorgement here also. The large bowel was healthy, but contained hard black masses of constipated faeces. The liver looked about normal in size, weighed 510 g., was not unduly flabby, and there was no pronounced wrinkling of the capsule. Both on the surface and on section this organ was in part bright yellow and in part reddish purple. The distribution of these areas was irregular and the normal liver markings had disappeared. The spleen was slightly enlarged, and there was a very small quantity of blood-stained fluid in the peritoneal cavity. The kidneys were in a state of advanced cloudy swelling, and in the pelvis of each there was a small quantity of bright-yellow crystalline material. The bladder contained 1/2 oz. (14 ml.) of cloudy urine which was not grossly bile-stained. The only abnormalities noted in the respiratory system were a few haemorrhages, each about 1/4 in. (0.6 cm.) in diameter, at the lung roots and some thick mucus in the bronchi.

The heart muscle was pale and there were two small subendocardial haemorrhages on the posterior wall of the left ventricle. Further haemorrhages, similar to those seen in the lungs, were noted at the lower pole of the thymus and along the descending thoracic aorta. All the other organs were normal.

Histology.—The liver showed degenerative changes ranging from cloudy swelling to complete necrosis. Some of the liver lobules had entirely disappeared, while in others the central cells still remained. Where the liver cells had vanished the capillaries were widely dilated and there were extensive areas of haemorrhage. General " polymorph " infiltration was in evidence, and deposits of granular pigment were scattered about. There was necrosis of the gastric mucosa to varying depths. Throughout the stomach wall the vessels were intensely engorged and there were haemorrhages between the muscle layers. The submucous layer was infiltrated with " polymorphs," and in places there were minute abscesses. The tubules of the kidneys and the heart muscle showed cloudy swelling. The lungs were acutely congested and there was some oedema. Desquamated epithelium and red cells were present in the bronchi.

Chemical Analysis.—The liver and the bowel and its contents were wet-ashed with nitric and sulphuric acids. The copper in the residue was determined polarographically, using a Tinsley recording polarograph, with the following results: liver 11.2 mg., bowel 5 mg. The manganese was determined by converting it to permanganate ion and measuring the absorption in a Hilger-Spekker absorptiometer. The following results were obtained: liver, 4.2 mg. ; bowel, 8 mg.

Case 2

At 7.15 p.m. on Sept. 9, 1946, a 1-year-old boy swallowed a quantity of the same proprietary preparation as in Case 1. It is estimated that he took between 30 and 35 tablets. The mother at once gave him salt and water, and when this failed to produce emesis she inserted her fingers into his throat and he vomited undigested food and a number of the tablets. Shortly afterwards the boy returned some brown material, and within an hour fresh and clotted blood. The child was admitted to hospital 90 minutes after taking the tablets.

On admission he was pale, collapsed, and shocked, with laboured, noisy, moist, and bubbly breathing. The pulse was thin and rapid, the rate being 170 a minute. There were dark-brown stains on his mouth resembling dried altered blood. The percussion note of his chest was unimpaired and moist breath sounds were heard at all areas. All other systems appeared to be normal. On admission to the ward the child started retching and when held up by his feet he vomited about 1 oz. (28 ml.) of fresh bright-red blood mixed with mucus. Immediate treatment was given to counteract the shock, warmth being applied externally. Gastric lavage was considered to be contraindicated, and bland fluids were given in the shape of milk and iced water. His general condition improved, and after a minim (0.06 ml.) of nepenthe at 10.15 p.m. he went to sleep. Four hours after admission the child again collapsed and appeared *in extremis.* The only positive findings were moist sounds in the chest and indications that the bronchial tree was full of fluid—presumably aspirated vomit. Intranasal oxygen was given, with slight improvement. The tablets in question were found to be radio-opaque, and the neck, chest, and abdomen were radiographed to determine whether any tablets could be seen in the stomach, bowel, or respiratory passages. None was observed. Atropine 1/150 gr. (0.43 mg.) was given at 4.5 a.m. on Sept. 10 and the child seemed slightly improved, but during the forenoon his temperature rose to 103° F. (39.4° C.). On the ground that an aspiration pneumonia was developing, a course of penicillin was started at 12 noon, with the result that the temperature began to fall. During the day there was one bowel action, the stool being very dark brown and offensive. At 6 p.m. the child again collapsed and vomited a small quantity of reddish-brown fluid. He was placed in an oxygen tent, but he died at 1.30 a.m. on Sept. 11— that is, about 30 hours after taking the tablets.

Post-mortem Examination.—This was carried out 34 hours after death. There was no jaundice. The only positive finding externally was the presence of a blotchy rash on the abdominal wall. The trachea and bronchi were filled with thick greenish

fluid which, from its colour, obviously contained some of the pigmented coating of the tablets. Both lungs were congested, and in them there were areas of collapse and a few scattered small haemorrhages. There were a few areas of pneumonic consolidation in the lower lobe of the right lung. The stomach was empty. Under the peritoneum covering it some haemorrhages could be seen. The lining of the stomach was brown, due to necrosis of the mucous membrane. The small bowel was normal, apart from an occasional area where the vessels were engorged. The large bowel was healthy and the contents of the bowel were stained black. The liver weighed 354 g. and its capsule was smooth. The liver tissue was yellow, but there were no haemorrhagic areas. Cloudy swelling of the kidneys was present. The urine contained no bile and no leucine or tyrosine crystals. The other organs were free from abnormality.

Histology.—The liver showed cloudy swelling and some fatty degeneration, but no necrosis. The gastric mucosa was necrotic to various depths, and much of the necrotic lining had been shed. The whole wall was intensely congested and there were extensive areas of haemorrhage in all its layers. In the submucous layer accumulations of " polymorphs " could be seen. The sections of the lung showed a typical bronchopneumonia. Cloudy swelling of the pancreas and kidneys was noted.

Chemical Analysis.—The liver and the bowel and its contents were analysed by the same method as was used in Case 1, with the following results: copper in liver, 2.88 mg.; in bowel. 4.58 mg.; manganese in liver, 1.375 mg.; in bowel, 3.56 mg.

Comment on Analysis

Quite a number of estimations of the normal copper content of the liver have been made, and a few of those published have been summarized in Table I. Many of the

TABLE I.—*Normal Copper Content of Liver*

Authority		Age	Copper per kg. of Liver	
			Fresh	Dry
			mg.	mg.
Sheldon and Ramage (1931)	{	Foetus	(37·5)	150
		Adult	(11·2)	45
Lesné, Zizine, and Briskas (1936)	{	Infants under 2 years	14·0	—
		Children 2–14 years	11·5	—
Cunningham (1931)		Adult	(6·2)	24·9
Brückmann and Zondek (1939)	{	Infants to 6 weeks	(57·5)	230
		Adults	(8·65)	34·6
Cited by Brückmann and Zondek:				
Ramage *et al.* (1933)	{	Infants to 7 weeks	(66·2)	265
		Children 3–12 years	(15·0)	60
Kleinmann and Klinke (1930)		Adults	(6·9)	27·5
Herkel (1930)		,,	(6·4)	25·4
Tompsett (1935)			(5·5)	22·0
Morrison and Nash (1930)	{	Children 3–12 years	9·03	—
		Infants to 2 years	24·0	—
		Adults	5·86	—

figures are given in terms of milligrams of copper per kilogram of dried tissue. The human liver contains approximately 75% of water (Gordon and Rabinowitch, 1933), and on this basis the figures quoted for dry tissue have been converted to milligrams of copper per kilogram of fresh liver. These figures are shown in parenthesis in Table I. It is at once apparent that there is a considerable variability in the results. This is due to two factors. First, the series of estimations was in most cases too short to strike a reliable average, as in any biological variable there is considerable deviation on either side of the mean ; and, secondly, the copper content of the foetal and infant liver is considerably in excess of that of the adult (Sheldon and Ramage, 1931). From the figures quoted the average for infants up to 2 years is 40.4 mg. per kg. of fresh liver ; for children from 2 to 14 years, 11.8 mg. per kg. ; and for adults 7.2 mg. per kg.

In Table II some estimations of the manganese content of the liver are quoted. It seems that this element is present in fairly constant amounts, and that there is no storage in infancy (Brückmann and Zondek, 1939). The average content per kilogram of fresh liver is 1.8 mg.

TABLE II.—*Normal Manganese Content of Liver*

Authority	Manganese per kg. of Liver	
	Fresh	Dry
Brückmann and Zondek (1939)	(1·75 mg.)	7·0 mg.
Cited by Brückmann and Zondek:		
Ramage *et al.* (1933)	(2·1 mg.)	8·4 mg.
Richards (1930)	1·75 mg.	—
Reiman and Minot (1920)	1·70 mg.	

Table III shows the content of manganese and copper per kilogram of fresh liver in the two cases under consideration. There seems to be no parallel between the

TABLE III.—*Manganese and Copper Content of Liver in Cases 1 and 2*

	Liver Weight	Copper per kg. of Liver	Manganese per kg. of Liver
Case 1	510 g.	21·9 mg.	8·2 mg.
,, 2	354 g.	8·1 mg.	3·9 mg.

two. In Case 1 the liver contains about twice the amount of copper expected, and in Case 2 only a fifth of the normal average. In Case 1 the manganese in the liver is over four times the normal, while in Case 2 it is only twice. No reasonable conclusions regarding the passage of the absorbed copper to the liver can be drawn, because of the relatively small amounts ingested and the variability in the normal content in young children. In both instances the manganese content was substantially increased, which suggests that, as the basic figure is more constant, this element tends to pass to the liver.

Animal Experiments

In order to determine with certainty which of the ingredients of the preparation in question was responsible for the death of these two children, a number of animal feeding experiments were undertaken. Guinea-pigs and cats were used. In the first instance six pairs of guinea-pigs were treated with the tablets. One pair served as controls and were given 6 ml. of water only. The remainder were dealt with in pairs with 5, 4, 3, 2, and 1 tablet respectively. Those given two tablets at 3 p.m. one day were all found dead next day at 9.30 a.m. The post-mortem findings were similar in all cases. The stomach showed a bluish-green patch on the greater curvature, and was distended with granular coffee-ground material heavily stained with fresh blood. The mucosa was brown and necrotic, and patches of it had been shed. Haemorrhages could be seen with the naked eye in the stomach wall. The upper part of the small bowel was injected and the contents were blood-stained. The large bowel and its contents were normal. and the animals did not suffer from diarrhoea. The liver appeared normal and no abnormalities, apart from occasional haemorrhages on the lungs and pericardium, were noted elsewhere.

Histological examination of the stomach showed necrosis of the mucous membrane to varying depths, with detachment of the more superficial layers. The vessels were engorged and haemorrhages could be seen in the submucous and muscular layers. " Polymorph " infiltration of the submucosa was noted. No wholesale necrosis was seen in the sections of the liver, the commonest appearance being cloudy swelling. Some vacuolation of the cells was not uncommon, and this was more in evidence in those animals given the larger doses. Here the cytoplasm appeared granular and fragmentary, and sometimes the cell contained a nucleus isolated in a large vacuole surrounded by an intact cell membrane. These areas were irregularly scattered and did not bear any special relation to the portal canals. " Polymorph " accumulations in the liver sinuses were not uncommon, but the groups usually

amounted to no more than a half-dozen cells. No significant histological changes were observed in any of the other tissues.

The two controls and the two guinea-pigs given one tablet each remained apparently unaffected. One control and one of the other animals died later from bronchopneumonia. All four animals were dissected, and no abnormality was discovered in the gastro-intestinal tract.

Two cats were each given five tablets, and within a short time they became ill and vomited blood. One of the cats was killed 4¼ hours later. The other cat survived but was ill for several days. It refused food, had no energy, and its coat was ragged. It had apparently completely recovered 18 days later when it was destroyed. The post-mortem examination of the first cat revealed naked-eye and microscopical changes in the stomach identical with those found in the guinea-pigs. All the other organs, including the liver, were normal. The second cat appeared to be perfectly healthy at necropsy, and there was no histological abnormality of the stomach. Sections of the liver, however, showed changes similar to those seen in the guinea-pigs given the heavier dosage. Many areas looked healthy, while in others the cells were in various stages of degeneration up to complete necrosis. There were no large areas of necrosis, but rather small nests of cells here and there surrounded by healthy liver tissue. No regenerative processes were seen.

At this stage of the investigation it was apparent that when a certain dose of this preparation was exceeded it was relatively lethal to cats and guinea-pigs. To determine which ingredient was the noxious one, it was decided to administer them separately to a further batch of animals. To begin with, ferrous sulphate was used alone. This was given to four pairs of guinea-pigs in doses of 3 gr. (0.2 g.) each to the first pair, 6 gr. (0.4 g.) to the second, 9 gr. (0.6 g.) to the third, and 12 gr. (0.8 g.) to the fourth. One of the guinea-pigs given 3 gr. died in 5 hours, the other survived, as did the pair given 6 gr., while those given 9 and 12 gr. died overnight. The post-mortem findings were identical to those observed in the guinea-pigs previously treated with the proprietary tablets. The animal killed by 3 gr. of ferrous sulphate weighed only 210 g. while its mate weighed 445 g. ; the pair given 6 gr. weighed 675 and 770 g. On considering those guinea-pigs killed by the smaller doses we find that, on an average, 1 gr. (0.065 g.) of ferrous sulphate per 64 g. body weight will prove fatal (Table IV).

TABLE IV

Weight of Guinea-pig	Dose of Ferrous Sulphate	Guinea-pig Weight per Grain of Ferrous Sulphate
416 g.	6 gr. (0·4 g.)	69 g.
355 g.	6 gr. (0·4 g.)	59 g.
210 g.	3 gr. (0·2 g.)	70 g.
535 g.	9 gr. (0·6 g.)	60 g.
560 g.	9 gr. (0·6 g.)	62 g.
	Mean:	64

The fact that the ferrous sulphate alone had the same effect and produced pathological changes identical with those occasioned by the proprietary tablets suggests strongly that the iron salt is the noxious ingredient. It was therefore decided to give six fresh guinea-pigs manganese sulphate and copper sulphate together. The proprietary tablets contain 1/75 gr. (0.87 mg.) of these salts for each grain of ferrous sulphate, and it was found that about 1 gr. of ferrous sulphate per 64 g. body weight of guinea-pig would prove fatal. The first pair were given 1/75 gr. of the manganese and copper salts per 64 g. body weight, the second pair double that amount, and the third pair a

triple dose. This treatment had no effect of any sort on the guinea-pigs. It would appear, therefore, that the two children and the experimental animals died from acute ferrous sulphate poisoning.

Conclusions

The proprietary preparation in question is widely used therapeutically and is generally regarded as being quite innocuous. This may be true in ordinary doses, but the two cases described and the results of the animal experiments clearly show that in very large doses this preparation may be highly dangerous. It is clear that these are cases of acute ferrous sulphate poisoning. This salt, in contact with the gastric juice, would be converted into the chloride, which has a considerable irritant action. This accounts for the acute haemorrhagic gastritis found in the two children and in the animals. The remarkable feature of Case 1 was the extreme liver damage found. We failed to produce comparable lesions in the experimental animals. Of course, in their case death occurred quickly, while the elder boy lived for 53 hours after taking the tablets. This allowed time for considerable toxic absorption from the damaged tissues of the stomach, and this alone may have been sufficient to produce the degree of liver destruction found. The younger boy lived for 30 hours, and in his case the liver damage was not nearly so great. He died from an aspiration pneumonia, and had he not contracted this he might well have recovered. The quantities of copper and manganese taken were too minute to have any toxic effect.

Summary

The toxicology of the salts of iron, copper, and manganese is briefly reviewed.

Two cases of fatal acute poisoning due to a proprietary preparation containing ferrous sulphate, manganese sulphate, and copper sulphate are described.

The results of a chemical analysis of the liver and of the bowel and its contents are given in each case.

A short series of animal feeding experiments is described, proving that the ferrous sulphate is the noxious ingredient in the preparation concerned.

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