FATAL POISONING OF AN INFANT BY ANTI-ANAEMIC PILLS CONTAINING IRON, MANGANESE, AND COPPER

BY

J. H. PRAIN, M.B., Ch.B.

(From the Department of Pathology, University of St. Andrews, and Royal Infirmary, Dundee)

[WITH PHOTOGRAVURE PLATE]

The use of iron in therapy dates back to Celsus, who treated splenomegalic anaemia by the administration of the water in which smiths had drenched their red-hot irons. It was not until 1746, however, that Menghinis discovered the presence of iron in the blood and so gave a reason for a form of therapy which has come into active use only within the last two generations. The benefits of vigorous ferro-therapy in special instances are so striking that iron is now too often used as treatment for any anaemic condition. More recently it has been found that traces of copper and manganese are necessary adjuvants in iron therapy, and the three metals are now available in the form of pills which are stable, effective, and elegant. There is little doubt that these pills are prescribed very frequently, as is shown by the fact that in this region, with a population of approximately 400,000, the five main hospitals issued approximately 500,000 of these pills in a period of six months. Unfortunately, the figures of the quantity prescribed by the practitioners are not available.

That ingested iron is not without danger is seen in Kachin Beck disease (Hiyeda, 1939), a disease occurring among children in Manchukuo and North Korea, due to continuous chronic overdosage with iron in the drinking-water. Acute overdosage by ingestion of pills containing iron, manganese, and copper has been recorded as causing death in three infants (Forbes, 1947; Thomson, 1947). The present case is presented because it allowed the investigation of certain points not available for study in the earlier cases, and its occurrence emphasizes again the need for every doctor and pharmacist, when supplying such pills (e.g., fersolate), to warn the mother of the extreme danger to infants.

Case Report

At approximately 7.30 p.m. on February 8, 1948, a girl aged 11 months swallowed some pills with which she had been playing. Each of the pills contained ferrous sulph. exsic. 3 gr. (0.2 g.), copper sulphate 1/25 gr. (2.6 mg.), and manganese sulphate 1/25 gr. (2.6 mg.). The exact number swallowed is unfortunately not known, as the mother seized the remainder and threw them in the fire. The child became very drowsy and vomited. The vomit was at first green and later became brown. She was admitted to Dundee Royal Infirmary at 9.30 p.m.—i.e., two hours after ingestion of the pills.

On admission she was pale and drowsy, but not cyanosed; she made no resistance to examination. The pulse was rapid but regular, the respiratory system seemed normal, the abdomen was soft and nowhere tender, the pupils reacted normally, and there was no evidence of neck rigidity.

Shortly after admission she vomited, the vomitus being brown in colour and streaked with bright-red blood, but there was no further vomiting after 10 o'clock that evening. She was treated immediately on admission with chalk mixture and sodium bicarbonate.

The next day she seemed to be much better, sitting up in her cot, taking notice of her surroundings, and playing with her toys. Two dark tarry stools were passed during the day, but there was no diarrhoea. On the morning of the 10th she was found to be much worse, with cyanosis of the lips and moist accompaniments to the breath sounds at both bases. Sulphadimidine ("sulphamezathine") and penicillin were given, but her condition deteriorated rapidly and she died at 1.10 p.m., 39 hours after ingestion of the pills.

Post-mortem Examination Report (21 hours after death).—"The body is that of an adequately nourished infant with slight cyanosis of the lips but no jaundice in skin or conjunctivae. The *stomach* shows an area of extreme congestion, containing numerous small haemorrhagic points with some oedema, and closer study reveals that in this area mucosal damage of varied degree is present. This area is situated in the middle third of the stomach, nearer the greater curvature, and extending upwards on the anterior and posterior walls. From this central area of intense change a lessening degree of reaction spreads over the remainder of the stomach. The stomach contains approximately 15 ml. of dark-brown coffee-ground material. In the *small intestine* there are a few areas of congestion and swelling, but this is not so marked as in the stomach; the three main areas of reaction are situated on the anterior wall of the third part of the duodenum, in the proximal jejunum, and as a diffuse slightly affected area in the proximal ileum. It is noted that the Peyer's patches are not affected. The ileum contains dark tarry faecal material. The *liver* (2 lb., or 0.9 kg.) is pale, flabby, and greasy to touch. The *spleen*, which is normal in size, weight, and consistence, presents a mottled appearance, light spots flecking the cut surface.

"The *lungs* show a considerable degree of congestion, and in the right upper lobe a small area of haemorrhage is present on the anterior border. The *heart* shows dilatation of the right auricle and ventricle, and the myocardium is generally soft and flabby. The valves are competent. The *pericardium* and *thymus* seem normal, as do the *gall-bladder, pancreas,* and *suprarenals.* The *kidneys* are pale, but apart from this appear healthy, with normal ureters; the bladder, which is also normal, contains 18 ml. of clear urine. The *reproductive organs* are normal, as are the *brain* and *meninges.*"

Special Examinations.—Analysis of the urine, gastric and caecal contents, and the bile for iron, copper, and manganese resulted as follows:

	Gastric Contents	Caecal Contents	Bile	Urine
Fe	0·455%	0·529%	0·0158%	0·0037%
Cu	0·0099%	0·00235%	0·00452%	0·000044%
Mn	Present	0·0024%	0·0057%	None

That the high gastric and caecal iron content is not entirely the result of the haemorrhage from the mucosal damage is shown by the presence of copper and manganese in the same samples. The "metabolic route" of the manganese is indicated by its obvious presence in the bile and its absence from the urine; the copper content of both bile and urine agrees with its recognized route of excretion. Since these estimations were made on isolated specimens obtained at necropsy it is unwise to compare them with normal excretion values, but they are much higher than those considered normal.

Histology.—The main lesions occur in the gastro-intestinal tract. In the stomach, the area of acute gastritis described above is seen to consist of localized areas of severe necrosis (Plate, Fig. 1) of the gastric mucosa with a striking impregnation of the adjacent reticulum by iron (Fig. 2), recalling the impregnation described in the pulmonary reticulum in haemosiderosis (Scott Park *et al.*, 1947). There is also oedema of the submucosa, and under the areas of necrosis the veins show thrombosis with iron impregnation of their walls (Fig. 3). Deeper still, the as yet not thrombosed vessels show thickened endothelium which contains masses of iron granules. The liver (Fig. 4) shows a widespread and surprisingly uniform fatty change and some iron is present, but in no great amount—much less than used to be seen in the typical case of pernicious anaemia. The presence of copper and manganese in the liver can perhaps be deduced from the fact that the reaction with sulphide shows more metal in the hepatic cells than is revealed

by Perls's reaction for iron. The tubules of the kidney show cloudy swelling but no other lesion, and iron could not be demonstrated. The only other significant finding in the viscera was necrosis of the Malpighian corpuscles of the spleen.

Discussion

Although previous reports have dealt with the toxicology of this condition, this new case raises some points in the clinico-pathological synthesis that are of interest.

It appears from the microscopical examination that once the gastric mucosa is damaged the iron escapes from the lumen into the tissues and leads to thrombosis of the submucosal veins; this thrombosis would seem to act as a block, in that comparatively little iron has been found in the liver. None the less, it is difficult to escape the conclusion that the gross fatty change in the liver is due to absorption of substances from the lumen through the areas denuded of mucosa, or possibly from the breakdown products of the mucosa itself. The extent and degree of the change in the liver seem scarcely sufficient to explain the fatal issue, but in view of the failure to find any other cause of death one might assume that the damaged liver, although capable of sustaining life for some time, was not capable of maintaining its detoxicating process in the continued presence of this absorption. The final collapse of the liver, by allowing access of the absorbed substances to the rest of the body, led to the sudden exitus. The necrosis of the Malpighian corpuscles is probably associated with that generalized toxaemia.

The present case emphasizes again two important clinical points. First, it is of the utmost importance to begin treatment urgently for the sake of the gastric mucosa, as it seems probable that the gastric mucosa is the first and main line of defence of the liver. In this respect it is of interest to note that a recent paper described a case of recovery after the ingestion of similar pills in which treatment was started at once by the patient himself, and little evidence of liver damage could be found (Roxburgh, 1949). The histological findings in the present case fail to provide any suggestions for specific therapy, and one can merely repeat the probable value of early administration of alkali to form insoluble hydroxides. It would seem that dimercaptopropanol (BAL) is unlikely to be of help (McCance and Widdowson, 1946) in such cases; it was used by Roxburgh, who makes no claim, however, for its value.

The second point of clinical importance is the occurrence of a misleading period of improvement and apparent well-being before a rapidly fatal termination. A similar false recovery occurred in one of Forbes's cases, and the fact should perhaps be stressed that in treatment of such cases this period of betterment neither lessens the gravity of the prognosis nor permits any relaxation of therapeutic activity.

Summary

A case is described of fatal poisoning of an infant by pills containing iron, copper, and manganese.

The clinical course showed a period of apparent recovery followed by sudden death: this misleading sequence occurred also in one of the previously reported cases.

The histological findings suggest that the destruction of the gastric mucosa leads to lethal hepatic damage.

It is the duty of doctors and pharmacists to warn parents of the grave risk to infants presented by these visually attractive pills.

I wish to thank Professor A. C. Lendrum for his help and advice in the preparation of this paper and Mr. A. Dargie, Dundee City Analyst, for the analysis of the specimens of gastric and caecal content, bile, and urine. I am also grateful to Dr. J. Thomson, Royal Infirmary, Dundee, for the clinical details, and to Mr. J. W. Corkhill for the photomicrography.

References

Celsus, A. C. (? A.D. 200). *De Medicina.* Liber 4, Cap. 9.
Forbes, G. (1947). *British Medical Journal*, **1**, 367.
Hiyeda, K. (1939). *Jap. J. med. Sci.*, Sect. 5 (Path.), **4**, 91.
McCance, R. A., and Widdowson, F. M. (1946). *Nature*, **157**, 837.
Roxburgh, R. C. (1949). *Proc. R. Soc. Med.*, **42**, 85.
Scott Park, S. D., Scott, L. D. W., and Lendrum, A. C. (1947). *Brit. J. Radiol.*, n.s. **20**, 100.
Thomson, J. (1947). *British Medical Journal*, **1**, 640.

SYNOVIAL OSTEOCHONDROMATOSIS

TWO UNCOMMON EXAMPLES

BY

J. F. CURR, M.D., F.R.C.S.Ed.

Formerly Temporary Assistant Surgeon, Royal Infirmary, and Leith Hospital, Edinburgh; late Orthopaedic Specialist, R.A.M.C.

[WITH PHOTOGRAVURE PLATE]

Synovial osteochondromatosis is a well-recognized condition, but the two cases reported here presented some unusual features.

Case 1

The patient, a man aged 23, had a history of stiffness of the right shoulder for about six months, associated with occasional slight pain, but with no obvious cause beyond some trivial injuries in the past. On examination there was a complete absence of any movement in the right shoulder-joint.

Radiological examination disclosed enormous numbers of opaque loose bodies, of varying size and density, occupying the entire shoulder-joint and extending into the subscapular bursa and the synovial sheath of the long head of the biceps. Synovial osteochondromatosis was diagnosed (Plate, Fig. 1). There was no abnormality elsewhere.

At operation the right shoulder-joint was exposed through a long anterior incision. On opening the bulging synovial membrane loose bodies were scooped out by the dozen, but many

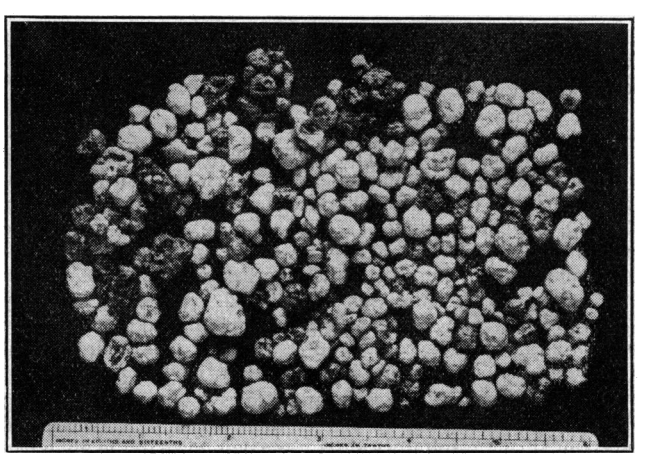

FIG. A.—Case 1. Photograph of loose bodies after removal.

still attached to it had to be avulsed or dissected out. An attempt at synovectomy was abandoned owing to tough adhesions and haemorrhage, but the whole of the synovial sheath of the long head of the biceps was excised and also as much as possible at the site of the reflection of the synovial membrane on the humerus. All loose bodies were removed after a complete exploration.

J. H. PRAIN: FATAL POISONING OF AN INFANT BY ANTI-ANAEMIC PILLS CONTAINING IRON, MANGANESE, AND COPPER

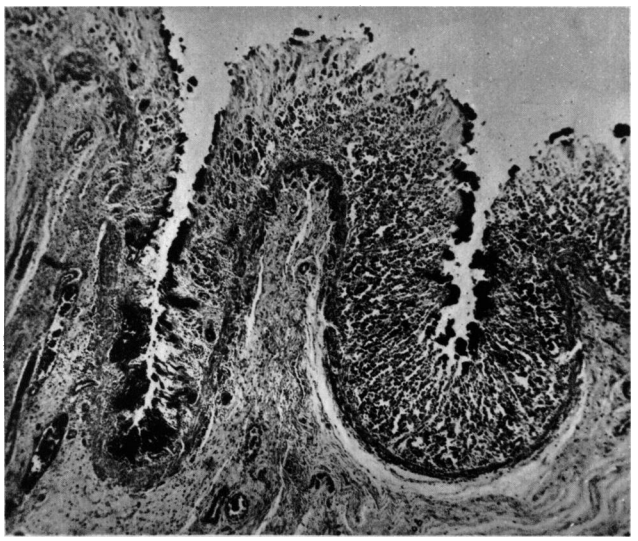

FIG. 1.—Gastric mucosa showing in left crypt necrosis with heavy impregnation by iron. In right crypt only surface layer is involved. Perles's method. (× 40.)

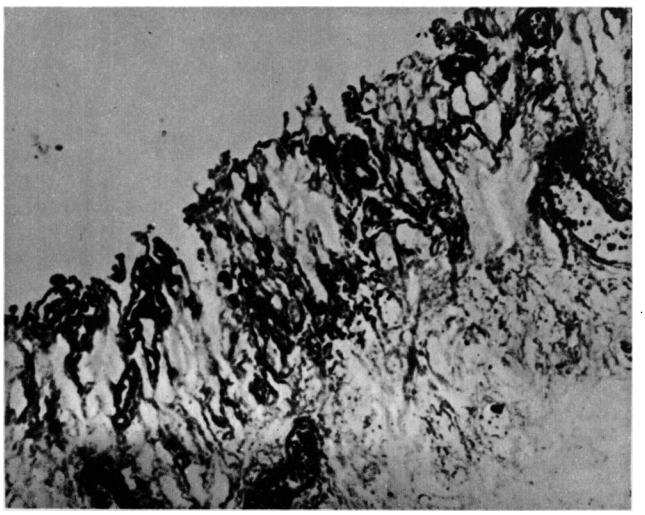

FIG. 2.—Damaged gastric mucosa showing impregnation of reticulum by iron. Perles's method. (× 80.)

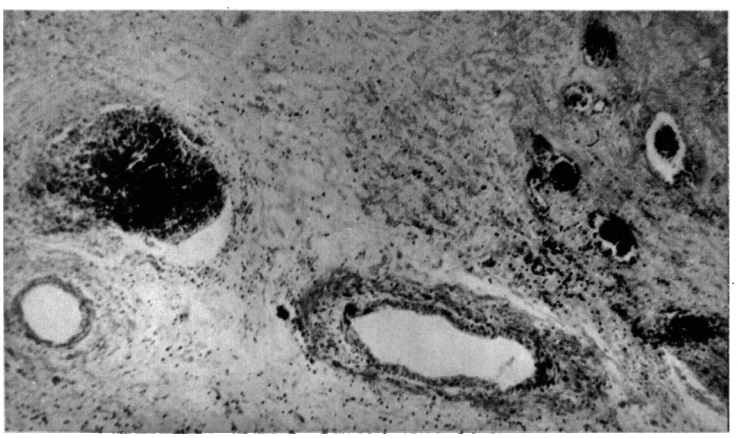

FIG. 3.—Thrombosis in veins of submucosa. Phloxine-tartrazine. (× 65.)

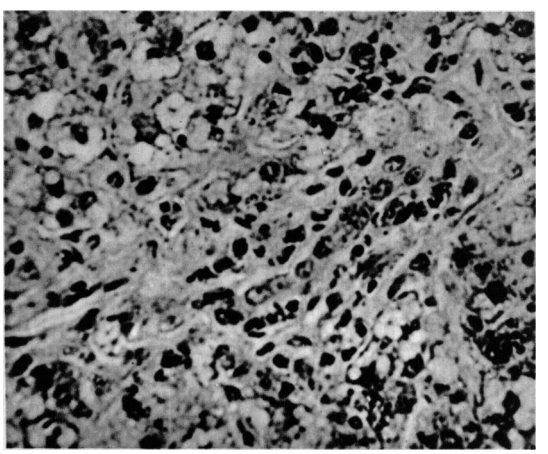

FIG. 4.—Liver showing fatty ballooning of cells. Celestin blue. (× 170.)

D. P. DEGENHARDT AND D. SHEEHAN: MULTIPLE MYELOMA

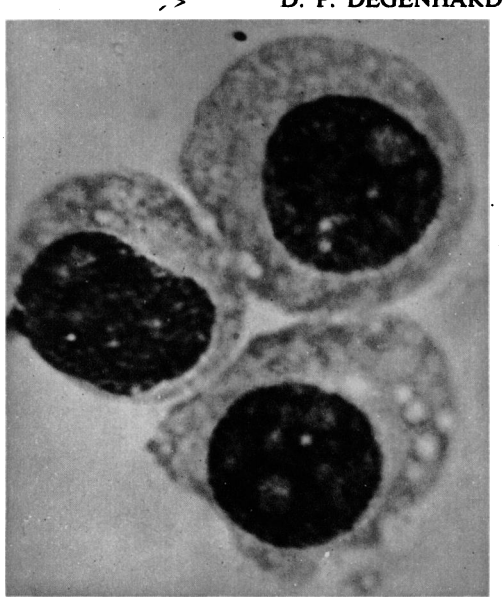

FIG. 1.—Case 5. Myeloma cells with scanty cytoplasm, vacuoles, and less densely staining nuclei with nucleoli. (1/12 objective.)

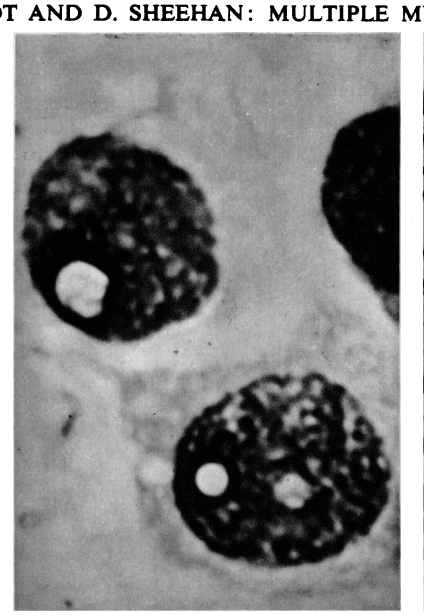

FIG. 2.—Case 6. Atypical myeloma cells with scanty cytoplasm. (1/12 objective.)

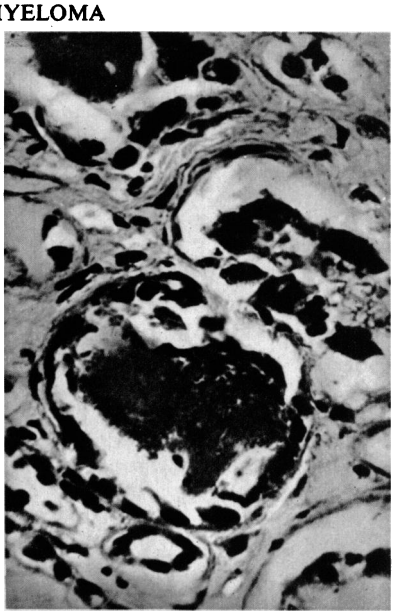

FIG. 3.—Case 4. Section of kidney showing blocking of tubules with eosinophil material and increase of interstitial tissue. (2/3 objective.)

Illustrations printed in Collogravure by HARRISON & SONS, LTD., Printers to His Majesty The King, London, Hayes (Middx.) and High Wycombe.