haemoglobin to methaemoglobin, which fixed the cyanide and prevented its toxic action (Wendel, 1933). However, despite this evidence, Steele and Spink (1933) used methylene blue in two cases of aniline poisoning with dramatic disappearance of methaemoglobinaemia, and Williams and Challis (1933) in one case. Subsequently Wendel (1937) agreed that it had this action in man in the dose used; and Hartman, Perley, and Barnett (1938) made a detailed study of it as an antidote for methaemoglobinaemia following sulphonamide therapy. Only two reports have been found of its use in nitrobenzene poisoning: Walterskirchen (1939) employed an unstated amount of 1% solution of methylene blue intravenously, and the cyanosis cleared in 15 minutes; and Leinoff (1936) gave 50 ml. of a 1% solution intravenously, and describes the patient as at first becoming darker blue, then within one hour the condition improved and the finger-nails became pink. He does not mention a return of the cyanosis, but this is implied in the subsequent statement that it disappeared completely in a few days. The dose given in the case reported here is much smaller than that advised by Hartman *et al.* (1938)—1–1.5 mg. per kg. The subsequent oral administration had less effect than would have been expected in view of the finding of the same workers that 1–2 gr. (0.065–0.13 g.) four-hourly controlled sulphonamide cyanosis. The use of ascorbic acid was suggested by Deeny, Murdock, and Rogan (1943), who reported on its use in congenital methaemoglobinaemia, and by Carnrick, Polis, and Klein (1946) in the acquired type, although in this case it was really given too late to say whether it was beneficial.

There does not seem to be any danger in giving methylene blue in these doses, although coloration of the urine may surprise the patient and injection outside the vein may cause a severe and painful inflammatory reaction.

Subsequently the extent of the haemolytic process must be watched, and, if the haematological or clinical condition demands it, blood transfusion should be given. In the present case it is probable that the haemolysis was maximal at the time of the transfusion and that the condition would have improved satisfactorily without it.

Summary

A case of acute nitrobenzene poisoning following oral ingestion is reported. Cyanosis and haemolytic anaemia were the outstanding clinical features. Methylene blue was used in the treatment of the methaemoglobinaemia, and the haemolytic anaemia was so severe as to need a blood transfusion.

I have to thank Dr. F. M. R. Walshe for permission to publish this case, and Dr. M. Maizels, Dr. M. E. Morgans, Dr. E. Roderic-Evans, and Mrs. C. E. Work for the investigations.

REFERENCES

- Adams, S. S. (1912). *Trans. Ass. Amer. Phys.*, **27**, 503.
 Adler, A. (1934). *Z. ges. Neurol. Psychiat.*, **150**, 341.
 Balsac, F. Heim de, Agasse-Lafont, E., and Feil, A. (1930). *Progr. méd., Paris*, **57**, 817.
 Bohland, K. (1919). *Dtsch. med. Wschr.*, **45**, 1388.
 Carnrick, M., Polis, B. D., and Klein, T. (1946). *Arch. intern. Med.*, **78**, 298.
 Carter, F. W. (1936). *Med. J. Aust.*, **2**, 558.
 Chapman, W. M., and Fox, C. G. (1945). *British Medical Journal*, **1**, 557.
 Deeny, J., Murdock, E. T., and Rogan, J. J. (1943). *Ibid.*, **1**, 721.
 Engel, H. (1934). *Occup. & Hlth.*, **2**, 334 (No. 286). Geneva.
 Ewer, H. (1920). *Dtsch. med. Wschr.*, **46**, 1078.
 Fullerton, W. W. (1930). *New Engl. J. Med.*, **203**, 423.
 Grafe, E., and Homburger, A. (1914). *Z. ges. Neurol. Psychiat.*, **25**, 343.
 Güntz, E. (1930). *Dtsch. Z. ges. gerichtl. Med.*, **15**, 461.
 Hamblin, D. O., and Mangelsdorff, A. F. (1938). *J. industr. Hyg.*, **20**, 523.
 Hamilton, A. (1919–20). *Ibid.*, **1**, 200.
 — (1921). U.S. Department of Labour, Bureau of Labour Statistics, *Bulletin*, No. 280.
 Hartman, A. F., Perley, A. M., and Barnett, H. L. (1938). *J. clin. Invest.*, **17**, 699.
 Hilbert (1915). *Dtsch. med. Wschr.*, **41**, 1115.
 Hogarth, C. W. (1912). *British Medical Journal*, **1**, 183.
 Leader, S. D. (1932). *Arch. Pediat.*, **49**, 245.
 Leinoff, H. D. (1936). *New Engl. J. Med.*, **215**, 191.
 Letheby, H. (1863–4). *Pharm. J. Trans.*, **5**, 2nd ser., 130.
 Levin, S. J. (1927). *J. Amer. med. Ass.*, **89**, 2178.
 — (1931). *Ibid.*, **96**, 681.
 Loeb, R. F., Bock, A. V., and Fitz, R. (1921). *Amer. J. med. Sci.*, **161**, 539.
 Meyer-München, E. (1905). *Berl. klin. Wschr.*, **42**, 1353.
 Muehlberger, C. W. (1925). *J. Amer. med. Ass.*, **84**, 1987.
 Nicholson, E. (1862). *Lancet*, **1**, 135.
 Nobécourt and Pichon, E. (1924). *Paris méd.*, **53**, 380.
 Rayner, W. (1886). *British Medical Journal*, **1**, 294.
 Schild, W. (1895). *Berl. klin. Wschr.*, **32**, 187.
 Schnopfhagen, H. (1927). *Wien. klin. Wschr.*, **40**, 998.
 Schultz (1915). *Münch. med. Wschr.*, **62**, 458.
 Scott, R. W., and Hanzlik, P. J. (1920). *J. Amer. med. Ass.*, **74**, 1000.
 Spinner, J. R. (1917). *KorrespBl. schweiz. Arz.*, **47**, 1439. Abstract in *J. Amer. med. Ass.*, **69**, 2155.
 Steele, C. W., and Spink, W. W. (1933). *New Engl. J. Med.*, **208**, 1152.
 Stevens, A. M. (1928). *J. Amer. med. Ass.*, **90**, 116.
 Stevenson, A., and Forbes, R. P. (1942). *J. Pediat.*, **21**, 224.
 Taylor, A. S. (1864). *Guy's Hosp. Rep.*, **10**, 193.
 Thomas, D. R. (1926). *Indian med. Gaz.*, **61**, 229.
 Thomsen (1921). *Münch. med. Wschr.*, **68**, 399.
 Walterskirchen, L. (1939). *Wien. klin. Wschr.*, **52**, 317.
 Wandel (1919). *Münch. med. Wschr.*, **66**, 1267.
 Wendel, W. B. (1933). *J. Amer. med. Ass.*, **100**, 1054.
 — (1937). *Ibid.*, **109**, 1216.
 Williams, J. R., and Challis, F. E. (1933). *J. Lab. clin. Med.*, **19**, 166.
 Wolpe, L. (1920). *Dtsch. med. Wschr.*, **46**, 100.

HETEROTOPIC OSSIFICATION OF AN APPENDICULAR MUCOCELE

BY

I. JUVARA, M.D., M.S.

Surgeon

AND

U. BORCESCU, M.D.

(From the Third Surgical Unit, Coltea Hospital, Bucharest, Rumania, under the Direction of Prof. D. Hortolomei)

By the term "heterotopic ossification" is meant the appearance of osseous tissue in an organ which has no ontogenetic relationship to the process of ossification. The spontaneous occurrence of heterotopic ossification has been observed in the most unexpected tissues and organs, as, for example, aneurysmal walls, old haematomata, laparotomy scars, injured muscles and nerves (Leriche and Policard, 1926), arterial walls (Mönckeberg, 1902), tonsils (Reitmann, 1903), aortic valves (Rosenstein, 1900), the anterior chambers of the eyes (Koch *et al.*, 1939), tissues affected by elephantiasis (Kleine, 1929), and of course tumours (Leriche and Policard, 1926; Törö, 1935).

Experimentally, the condition has been obtained by ligation of the renal vessels, in granulation tissue by a variety of methods (Leriche and Policard, 1926), by grafting a portion of gall-bladder mucosa, urinary-bladder mucosa, or even gastric mucosa into various connective tissues (Cavalli, 1939; Jung and Cemil, 1935; Leriche and Lucinisco, 1935; Lucinisco and Cavalli, 1935, 1936; Santa and Marcacci, 1938), or when a portion of an aponeurosis has been used to replace a defect in the urinary bladder wall (Neuhof, 1918–20; Huggins, 1931; Phemister; Copher and Key).

The mechanism of heterotopic ossification is still a matter of controversy. Conheim supported the theory of latent embryonic points of ossification; Ollier that of periosteal displacements; Busch, Macewen, and Ribbert that of the haematogenous seeding of osteoblasts. At present the hypothesis of Leriche and Policard is favoured—namely, that the principal requirements for the occurrence

FIG. 1.—Naked-eye appearance of the tumour.

FIG. 2.—From above downwards: smooth-muscle tissue with fragments of epithelium; granulation tissue, with areas of calcification; osseous tissue. (Mann's stain; ocular $\times 5$; objective No. 3, Zeiss.)

of heterotopic ossification are the creation of a granulation tissue and the deposit therein of calcium salts, these processes occurring either together or in succession.

Slowing down of the circulation, produced by venous stasis, is a factor in fibrous ossification. Ischaemia is a factor in enchondral ossification (Giuliani, 1934).

Our present work deals with a case of heterotopic ossification of a mucocele of the vermiform appendix. This had opened into the peritoneal cavity and was associated with a gelatinous condition of the peritoneum (Péan's disease or Werth's pseudo-mycomatosa peritonealis). The appendix was located in the sac of an inguinal hernia. The condition was discovered at an emergency operation for strangulation of the hernia.

Case Record

The patient, a man aged 70, was admitted to hospital on the afternoon of May 14, 1946, with strangulation of a right inguino-scrotal hernia. The hernia first appeared six years before and had since strangulated twice. On each occasion reduction of the hernia was successfully carried out after one or two hours. On May 14, immediately after a muscular effort, strangulation recurred, and repeated attempts by the patient to reduce the hernia were unsuccessful. He was admitted six hours after the onset of strangulation. On admission his general condition was found to be good. The bowels had moved, and an irreducible hard inguino-scrotal tumour was found on the right side.

Operation (Radical cure. Spinal "percaine" and ephedrine).—The sac was dissected out and the contents found to be stony hard.

On opening the sac an osseous body about 7 cm. long was found, bound to the omentum at its upper pole. With a view to determining the nature of this tumour the incision was extended superiorly and the abdomen opened, whereupon a large quantity of mucus flowed out through the abdominal incision. A gelatinous condition of the peritoneum secondary to rupture of an appendicular or other mucocele was suspected and the caeco-appendicular area was explored.

FIG. 3.—For description, see text. (Giemsa stain; Oil-immersion objective No. 60, Zeiss.)

The osseous body was found to be in direct connexion with a remnant of the appendix, approximately 1 cm. in length. The tumour and the appendicular remnant were removed and the operation finished by the method of Bassini.

Post-operative progress was normal and the patient was discharged after 12 days. A general examination of the patient six months later was satisfactory.

Pathological Examination of the Tumour.—The tumour (Fig. 1) was ellipsoidal in shape, about 7 cm. in length, opaque to x rays, and covered by soft tissues only over its upper pole. Microscopically it was seen to be a terminal atrophic portion of a vermiform appendix, with a tendency to sclerosis. The principal mass of the tumour consisted of three main histological elements—epithelium, granulation tissue, and osseous tissue (Fig. 2). The epithelium was of intestinal type and showed areas of hypertrophy and hyperplasia as well as of atrophy. These epithelial areas occurred in islands or in long strands. In some areas there were smooth-muscle fibres in relation to the epithelium. The lumen of the appendix, where it was still visible, was filled with an amorphous material which took up a rose-red colour when stained with Mayer's mucicarmine. The granulation tissue was situated between the epithelium and the osseous tissue. It showed areas of necrosis near the epithelium and of calcification near the osseous tissue. It could be clearly seen that calcium salts were being deposited in the necrotic areas, and that ossification was occurring in the calcified zones, where osteoblasts penetrated through connective-tissue trabeculae (Fig. 3). Peripherally the osseous tissue was contiguous with and external to the calcified zones. It contained typical bone

cells and medullary spaces having blood capillaries and scanty haemopoietic cells. The direction of the Sharpey fibres showed clearly that the osseous tissue had been subjected to continual mechanical stress.

Discussion

In retrospect the condition is considered to have been a perforated appendicular mucocele (in the sense used by Ferret in 1876) for the following reasons. There was a gelatinous condition of the peritoneum, and the pedicle of the tumour consisted of an appendicular remnant. On section the tumour showed portions of intestinal epithelium and mucous cavities.

The case can be considered to be a fortuitous experiment presenting the following features: the presence of an epithelium in a connective-tissue medium with a reduced circulation; mucoid impregnation of the whole structure; the development of a granulation tissue and of areas of necrosis in the wall of the appendix. The regular fibrillary structure shows, further, that some of the changes are due to traction or pressure by the intra-abdominal viscera, to intestinal peristalsis, and to traction by omental adhesions.

The role of the epithelium in heterotopic ossification is known from experiments. The experimental transplantation of mucous tissues into connective-tissue media constantly results in hypertrophy and proliferation of the mucous epithelium. Sometimes the epithelium may be responsible for the secretion of a phosphatase (Lucinesco and Cavalli, 1935, 1936; Severi, 1939). Zones of necrosis are the usual sites of calcification. The histiocytes of the granulation tissue represent the source of the osteoblasts. Physiological studies have long ago shown that mucous substances and mechanical irritants have an osteogenetic effect. But even now there is no explanation of how haemopoietic tissue develops in relation to areas of heterotopic ossification.

Perusal of the literature revealed reports of calcification in appendicular mucoceles (Henke and Lubarsch, 1929; Olanescu *et al.*, 1942) and of three cases of actual ossification (Henke and Lubarsch, 1929). Two of the latter were published by Nishii and Akimoto (1928)—appendicular carcinomata associated with mucoceles, where osseous tissue appeared only in areas free of the invading neoplasm. The third was published from the Virchow-Krankenhaus (680/1928)—a case of partial appendicular mucocele containing in its walls osseous foci showing a regular fibrillary structure.

Summary

A case of heterotopic ossification of an appendicular mucocele is reported. Ossification was of wide extent and was associated with the appearance of haemopoietic tissue. The mucocele had perforated and was accompanied by a gelatinous condition of the peritoneum. The various conditions required for the onset of ossification—structural, biochemical, and mechanical—were present and are discussed. The condition was not suspected clinically, being discovered only at operation.

BIBLIOGRAPHY

- Carone, C. (1936). *Ann. ital. Chir.*, **15**, 461.
Cavalli, G. F. (1939). *Arch. ital. Med. sper.*, **4**, 321.
Cruickshank, M. M. (1936). *Indian med. Gaz.*, **71**, 28.
Fratton, G. (1937). *Arch. ital. Chir.*, **45**, 301.
Giuliani, G. M. (1934). *Ibid.*, **38**, 645.
Guerrisi, A. (1938). *Folia med.*, Napoli, **24**, 1196.
Henke, F., and Lubarsch, O. (1929). *Handbuch der speziellen path. Anat. u. Histol.*, vol. IV/III, p. 533. J. Springer, Berlin.
Huggins, C. B. (1931). *Arch. Surg.*, Chicago, **22**, 377.
Jones, R. W., and Roberts, R. E. (1934). *Brit. J. Surg.*, **21**, 461.
Jung, A., and Cemil, S. (1935). *Presse méd.*, **43**, 140.
Kleine, H. O. (1929). *Arch. Gynäk.*, **139**, 145.
Koch, C., Schreiber, B., and Schreiber, G. (1939). *Ophthalmologica*, Basel, **97**, 284.
Leriche, R., and Lucinesco, E. (1935). *Presse méd.*, **43**, 137.
— and Policard, A. (1926). *Les Problèmes de la Physiologie Normale et Pathologique de l'Os*. Masson, Paris.

- Lucinesco, E., and Cavalli, G. (1935). *C. R. Soc. Biol.*, Paris, **120**, 139.
— (1936). *Arch. ital. Chir.*, **42**, 581.
Merlini, R. (1931). *Arch. ital. Anat. istol. pat.*, **2**, 1343.
Mönckeberg, J. G. (1902). *Virchows Arch.*, **167**, 191.
Neuhof, H. (1918–20). Studies from the Lab. of the Dep. of Surg., vol. III.
Nishii, R., and Akimoto, K. (1928). *Virchows Arch.*, **268**, 203.
Olanescu, G., Juvara, I., and Georgescu, C. (1942). *Rev. Chir., Bucuresti*, **622**.
Paggi, B. (1936). *Policlinico, sez. chir.*, **43**, 328.
Regen, E. M., and Wilkins, W. E. (1934). *J. Lab. clin. Med.*, **20**, 250.
Reitmann, K. (1903). *Msschr. Ohrenheilk.*, **34**, 321.
Rollo, S. (1931). *Riv. Biol.*, **13**, 14.
Rosenstein, P. (1900). *Virchows Arch.*, **162**, 100.
Santa, L., and Marcacci, G. (1938). *Arch. ital. Chir.*, **49**, 593.
Scheidegger, S. (1939). *Schweiz. Z. Path. Bakt.*, **2**, 153.
Severi, R. (1939). *Boll. Soc. ital. Biol. sper.*, **14**, 456.
Törö, I. (1935). *Anat. Anz.*, **80**, 285.
Wurm, H. (1930). *Beitr. path. Anat.*, **85**, 461.

Medical Memoranda

An Unusual Case of Large-Bowel Obstruction

The following case of large-bowel obstruction after perineal excision of the rectum merits recording on account of its rarity. A search of the literature failed to reveal a similar case.

CASE REPORT

A woman aged 54 was admitted to the wards of Mr. R. A. Keane at the North Staffordshire Royal Infirmary on Nov. 27, 1946, complaining of pain in the centre of the abdomen for three days. She had vomited on the morning of admission. A perineal excision of the rectum had been performed nine years previously and the colostomy had functioned adequately till one year ago, when a plastic operation was carried out for stenosis of the opening. Thereafter the colostomy had again functioned normally until two days before admission. There had been no bowel action since. There was also difficulty in micturition.

On examination the temperature was 98° F. (36.7° C.), pulse 88. The tongue was furred. The abdomen was soft, and a large median swelling was visible in the suprapubic region which was tender and resonant on percussion. Normal bowel sounds were heard and there was no evidence of intestinal colic during examination. A left inguinal colostomy was present which looked quite normal, but it was impossible to introduce a finger into either opening.

Operation. Under general anaesthesia—nitrous oxide, oxygen, "trilene," and ether—a right paramedian subumbilical incision was made. A gangrenous mass of large bowel presented in the wound. This proved to be the blind efferent loop of large bowel leading from the colostomy. It was not fixed distally to the pelvic floor, but hung free in the peritoneal cavity as a pendulous sac. This sac was about 8 by 3 in. (20 by 7.5 cm.) in size, had undergone torsion at its base, and was bluish in colour. This blind end of colon was resected, leaving about a 1½-in. (3.75-cm.) stump at the colostomy. Free blood-stained fluid was mopped out of the pelvis, revealing the uterus firmly attached to the sacrum by adhesions on its whole posterior surface. Sulphathiazole, 5 g., was inserted in the peritoneal cavity and the abdomen was closed with a stab drain to the pelvis. The colostomy acted profusely before the patient left the table. Examination of the specimen showed a black gangrenous mucosa; the sac of bowel contained a heavy, putty-like faecal mass about the size of an orange and with a most offensive odour. Convalescence was uneventful, and the patient was discharged home on the sixteenth day.

COMMENT

This unusual complication of perineal excision of the rectum could occur only where the distal segment of bowel was hanging free and was not fixed in the usual manner to the reconstituted pelvic floor. This and the adherence of the uterus to the sacrum suggest either that an inadequate repair of the pelvic peritoneum had been carried out or that it had broken down post-operatively. The weighty faecal mass was presumably a precipitating factor.

My thanks are due to Mr. R. A. Keane for permission to publish this case.

KENNETH G. F. MACKENZIE, M.B., F.R.C.S.,
Resident Surgical Officer,
North Staffordshire Royal Infirmary.