levels remained low in these patients during the secondary rise in excretion.

We believe these findings indicate a phase of post-operative hyperparathyroidism arising in the remaining parathyroid glands, which is due to the rapid fall of serum calcium following removal of the tumour.

We are grateful to Professor Russell Fraser, who has given much valuable advice, and under whose care six of the patients were. We also thank Miss Myra Low, Mrs. Ann Ross, and Mrs. Barbara Coates, who carried out many of the biochemical estimations.

REFERENCES

Albright, F., and Reifenstein, E. C., jun. (1948). *The Parathyroid Glands and Metabolic Bone Disease.* Williams and Wilkins, Baltimore.
Barnicot, N. A. (1948). *J. Anat. (Lond.)*, **82**, 233.
Chambers, E. L., jun., Gordan, G. S., Goldman, L., and Reifenstein, E. C., jun. (1956). *J. clin. Endocr.*, **16**, 1507.
Crawford, J. D., Osborne, M. M., jun., Talbot, N. B., Terry, M. L., and Morrill, M. F. (1950). *J. clin. Invest.*, **29**, 1448.
Fraser, R., and Harrison, M. T. (1960). To be published.
—— —— and Ibbertson, H. K. (1960). *Quart. J. Med.* In press.
Goldman, R., and Bassett, S. H. (1964). *J. clin. Invest.*, **33**, 1623.
Howard, J. E. (1956). *Ciba Foundation Symposium on Bone Structure and Metabolism*, p. 206, edited by G. E. W. Wolstenholme, and C. M. O'Connor. Churchill, London.
King, E. J., and Wootton, I. D. P. (1956). *Micro-analysis in Medical Biochemistry*, 3rd ed. Churchill, London.
MacIntyre, I. (1957) *Biochem. J.*, **67**, 164.
Milne, M. D., Stanbury, S. W., and Thomson, A. E. (1952). *Quart. J. Med.*, **21**, 61.
Nordin, B. E. C. (1958). *Advanc. intern. Med.*, **9**, 81.
—— and Fraser, R. (1954). *Clin. Sci.*, **13**, 477.
—— —— (1956). *Ciba Foundation Symposium on Bone Structure and Metabolism*, p. 222, edited by G. E. W. Wolstenholme and C. M. O'Connor. Churchill, London.
Roscoe, M. H (1953). *J. clin. Path.*, **6**, 201.
Schaaf, M., and Kyle, L. H. (1954). *Amer. J. med. Sci.*, **228**, 262.
Sirota, J. H. (1953). *Fed. Proc.*, **12**, 133.

PIGMENTATION OF JEJUNAL MUSCLE

BY

PAMELA M. FULLERTON, M.A., B.M., M.R.C.P.

Senior House Officer, Department of Morbid Anatomy, Central Middlesex Hospital, London

Recently pigmentation of intestinal muscle fibres has been increasingly recognized in steatorrhoea and other gastro-intestinal conditions. Fifty cases from the literature have been collected and eight new cases are described. Three of the new cases had secondary steatorrhoea, and among the eight are three cases of jejunal diverticulosis.

Of the 50 cases previously described, 25 definitely had steatorrhoea: 18 had idiopathic steatorrhoea or coeliac disease, 2 had Whipple's disease, 4 had jejunal diverticulosis, and 1 had chronic jejunitis (Pappenheimer and Victor, 1946; Adlersberg and Schein, 1947; Tverdy *et al.*, 1949; Paulley, 1954; Ansanelli and Lane, 1957; Himes and Adlersberg, 1957; Gresham *et al.*, 1958; Richards, 1959). Six cases recorded by Richards (1959) had local gastro-intestinal disease but no steatorrhoea. Two of these had hiatus herniae with oesophageal ulceration, two had duodenal ulcers with pyloric stenosis, one had had a partial gastrectomy, and one a duodenal lesion of uncertain aetiology. The presence or absence of steatorrhoea is not recorded in the other 19 cases. These comprise nine cases of fibrocystic disease of the pancreas, one of duodenal ulcer with gastro-colic fistula, three of malnutrition or malabsorption, aetiology not stated, four of idiopathic hypoproteinaemia, and two of Laennec's cirrhosis (Pappenheimer and Victor, 1946; Ansanelli and Lane, 1957; Schwartz and Jarnum, 1959). In experimental animals, similar pigmentation of intestinal muscle has been recorded in dogs with bile fistulae (Whipple and Hooper, 1917; Hooper and Whipple, 1917), and also in dogs that had been fed large amounts of whole liver or cod-liver oil (Nachtnebel, 1933).

The commonest opinion is that this pigment is a lipofuscin (Paulley, 1954; Schwartz and Jarnum, 1959; Gresham *et al.*, 1958) similar to the common "wear and tear" pigment or *Abnutzungspigment* that is found in heart muscle and liver with increasing age. Lipofuscin is thought to be derived from many unsaturated lipoids and lipoproteins by a process partly involving oxidation. The pigment is a heterogeneous collection of substances resulting from this breakdown.

Case Reports

Summary of Cases

Case No.	Diagnosis	Sex	Age	Bowel Habits	Weight
1	Jejunal diverticulosis	F	82	Steatorrhoea 31 g. fat/24 hrs	4 st. 4 lb. (27·2 kg.). Weight loss ++
2	Chronic pancreatitis	M	44	Steatorrhoea 74 g. fat/24 hrs	10 st. 5 lb. (65·8 kg.). History of some weight loss
3	Jejunal diverticulosis	M	71	Steatorrhoea 45 g. fat/24 hrs	9 st. 3 lb. (58·5 kg.). Gained 20 lb. (9 kg.) in one year post-op.
4	,, ,,	F	88	Normal	—
5	Ulceration of small intestine	F	54	Severe diarrhoea	4 st. 7 lb. (28·6 kg.). Weight loss ++
6	Portal cirrhosis	F	87	Normal	—
7	,, ,,	F	70	,,	—
8	Chronic peptic ulcer	M	75	,,	—

Case 1.—A woman aged 82 was admitted to hospital with hypertensive congestive cardiac failure. She was grossly emaciated, weighing 4 st. 4 lb. (27.2 kg.). She had a history of steatorrhoea for several months and was passing 31 g. of fat in 24-hour faeces. She died from recurrent chest infections. At necropsy gross diverticulosis of the small intestine was found. This was maximal in the jejunum but extended to the terminal ileum. The diverticula were of classical mesenteric distribution and up to 3 cm. in size. Pigmentation of the jejunum was noted macroscopically. Histologically, the muscle of the small intestine showed well-developed brownish granular pigmentation within the myofibrils. There was no pigment in the muscularis mucosae.

Case 2.—A man aged 44 had a partial gastrectomy for a duodenal ulcer, which had caused symptoms for 20 years. An abnormal pancreas was noted at this time. Five months later he had an attack of acute pancreatitis and then developed steatorrhoea, passing up to 74 g. of fat in 24-hour faeces. At further laparotomy the small intestine was seen to be yellowish brown and the pancreas hard and irregular, containing many small retention cysts. His steatorrhoea improved on pancreatin. A surgical biopsy of the jejunum showed numerous pigment granules in the cells of the muscularis propria. The villi of the intestinal mucosa were normal, supporting the pancreatic origin of his steatorrhoea (Shiner, 1959).

Case 3.—A 71-year-old man had dyspepsia for 17 years and steatorrhoea for six years, and was passing 45 g. fat in 24-hour faeces. He weighed 9 st. 3 lb. (58.5 kg.). At laparotomy diverticulosis was found, limited to the first 8 ft. (2.4 m.) of jejunum. This was resected. Since the resection his steatorrhoea has stopped, and he gained 20 lb. (9 kg.) in the first year. Microscopy of the jejunum showed widespread pigment in the fibres of the muscularis propria.

Case 4.—A woman aged 88 was admitted with a perforated duodenal ulcer. This was sutured, but she died on the 12th post-operative day. There was no history of steatorrhoea or evidence of loss of weight. At necropsy two chronic gastric ulcers were seen, as well as the recently perforated duodenal ulcer. Of interest was the finding of extensive diverticulosis of the small intestine, maximal in the jejunum. Histological examination showed a moderate amount of pigment in the cells of the muscularis propria of the jejunum.

Case 5.—A woman aged 54 was admitted with a history of one year's severe diarrhoea and loss of weight. She was emaciated, weighing 4 st. 7 lb. (28.6 kg.), and anaemic (Hb 38%). No pathogenic organisms grown on stool culture. She died 10 days later. At necropsy superficial ulceration of the whole of the small intestine, maximal in the terminal ileum, was found, but no ulceration of the large intestine. The final diagnosis could not be more definite than intestinal ulceration of unknown aetiology. Histological examination revealed scanty pigment granules in some of the fibres of the muscularis propria.

Case 6.—A woman aged 87 was admitted with oedema and ascites. There was no history of steatorrhoea or loss of weight. She died shortly after admission. At necropsy portal cirrhosis was found. The mesentery and intestine were oedematous but otherwise macroscopically normal. Histological examination of the jejunum showed pigment granules in a number of the muscle fibres.

Case 7.—A woman aged 70 was admitted with ascites; she lapsed into coma and died. At necropsy portal cirrhosis was found. The intestine was macroscopically normal. On microscopical examination pigment granules were seen in the muscle fibres of the jejunum.

Case 8.—A man aged 75 died of haemorrhage from chronic peptic ulceration of a gastro-enterostomy stoma. There was a 20-year history of duodenal ulceration, treated by gastro-enterostomy 10 years before death. There had been repeated haemorrhages into the gastro-intestinal tract, but no other abnormality. At necropsy the proximal jejunum was seen to be brown, and on microscopy the outer (longitudinal) smooth-muscle fibres were grossly pigmented.

Histology

In all these cases pigment was confined to the muscularis propria and none was found in the muscularis mucosae. This has been noted by others (Himes and Adlersberg, 1957; Gresham *et al.*, 1958). This is of interest because in this department over 100 jejunal biopsy specimens have been examined. These were taken with a jejunal biopsy tube (Shiner, 1957). Muscularis propria is, of course, absent from this material, but no pigment was found in the muscularis mucosae, which was routinely examined for it.

In many cells containing pigment the granules, which varied in size from 0.5 to 3 μ in diameter, occupied a large part of the myofibril, which was distended. When the pigment was scanty it was predominantly paranuclear. This situation was noted by Paulley (1954), and is seen in the lipofuscin of heart muscle.

These eight cases all had pigment with similar staining reactions. A positive reaction was obtained by the periodic-acid–Schiff technique, Fontana's silver method, and Mallory's haemofuscin stain. In addition, in all cases the pigment was partially acid-fast with Ziehl–Neelsen carbol-fuchsin method. In all sections the pigment gave a negative reaction on staining for iron. Several frozen sections were stained with oil red 0 and gave a positive reaction. These staining properties are characteristic of lipofuscin.

Discussion

Intestinal muscle pigment has now been described in a wide variety of diseases. In over half the recorded cases and in three of the eight described here there has been steatorrhoea, which has had many different causes. Thus steatorrhoea is common, but it is not always present. The finding of this pigment cannot, then, be of any diagnostic value as was suggested by Gresham *et al.* (1958), who thought it was confined to cases of idiopathic steatorrhoea.

There has been some abnormality of the gastro-intestinal tract in all the cases of intestinal pigmentation. Steatorrhoea or gross local disease has been present in most. In idiopathic hypoproteinaemia, though no structural abnormality has yet been seen, the intestine is not functionally normal. Loss of protein into the lumen has been demonstrated (Schwartz and Jarnum, 1959). In portal cirrhosis the intestine is subjected to an abnormally high venous pressure and often appears oedematous on post-mortem examination. Thus, in all the conditions in which intestinal muscle pigment has been described, there is probably some functional abnormality.

Several workers think that vitamin-E deficiency is important in the development of the pigment (Pappenheimer and Victor, 1946; Himes and Adlersberg, 1957). Ansanelli and Lane (1957) suggest that the mechanism might be uninhibited oxidation in the absence of the anti-oxidant action of vitamin E. In the case of idiopathic steatorrhoea described by Tverdy *et al.* (1949), and also in one described by Pappenheimer and Victor (1946), an associated testicular atrophy was present, which they take as further evidence of vitamin-E deficiency. However, in experimental vitamin-E deficiency in rats, though similar pigment granules develop in smooth-muscle fibres, they are not found in intestinal-tract muscle (Martin and Moore, 1939). Vitamin-E absorption might possibly be defective in all the conditions in which intestinal pigment has been found.

Lipofuscin in liver and heart muscle increases with age. In the present series, though three patients were over 80, the youngest was only 44. The patients described by Schwartz and Jarnum (1959) were aged 28, 30, and 34, and those of Pappenheimer and Victor (1946) were aged 32, 33, and 42. The cases of fibrocystic disease (Ansanelli and Lane, 1957) occurred in children. Thus pathological conditions seem to be more important than age. During this work intestinal muscle fibres have been examined for pigment in a number of unselected patients dying over the age of 90; no pigment was found. Again, unlike the lipofuscin in heart and liver, jejunal lipofuscin has not yet been demonstrated in the absence of gastro-intestinal disease.

In the present series two patients were grossly emaciated, and two gave a history of some loss of weight, but there was no obvious evidence of loss of weight in the other two. A few cases in the literature are described as emaciated, but many are not. Loss of weight alone does not seem to be important.

The pigment found in intestinal muscle has often been referred to as "ceroid" (Pappenheimer and Victor, 1946; Ansanelli and Lane, 1957). Ceroid was the name first given by Lillie *et al.* (1942) to the pigment found

in the livers of rats suffering from nutritional cirrhosis and studied in more detail by Endicott and Lillie (1944). Pearse (1953) says ; " I conclude, however, not only that ceroid is a mixture of substances, but that it represents a typical lipofuscin in an early stage of oxidation." The substances described as ceroid in intestinal muscle fibres seem to be similar to the pigment described here. On the basis of this and Pearse's (1953) comment it seems unnecessary to try to separate ceroid from lipofuscin.

There seems to be no relation between the pigment of jejunal muscle and that in melanosis coli. " Pseudomelanin " is found in the macrophages of the lamina propria of the mucous membrane. It is thought to be a protein degradation product absorbed from the large intestine (Stewart and Hickman, 1931). The distribution of muscular pigmentation of the small intestine does not suggest that it has been absorbed. It is absent from the macrophages of the mucosa and confined to the muscle fibres.

Some of the recorded cases of intestinal pigmentation have had similar pigment at other sites. Ansanelli and Lane (1957) found it in smooth-muscle fibres in blood-vessels of skeletal muscle and intestine, but not in striated-muscle fibres. The case described by Tverdy *et al.* (1949) also had pigment in smooth muscle of various arteries and in bronchial muscle fibres. Pappenheimer and Victor (1946) describe unusual amounts of pigment in various other organs in several cases—for example, testis, liver, kidney, adrenal cortex, and uterus. This pigment seems to be the same as that in the intestine. In many reports there was similar pigment in the stomach, ileum, and sometimes colon, though it was always maximal in the jejunum (Himes and Adlersberg, 1957 ; Gresham *et al.*, 1958). In the cases recorded here no excessive pigment was found at other sites in post-mortem specimens. Intestine other than jejunum was not examined. The widespread distribution of a similar type of pigment in some cases suggests a general metabolic disturbance rather than a purely local pathological change. It also supports the idea (Ansanelli and Lane, 1957) that the pigment is the result of disease and not its cause, as was suggested by Gresham *et al.* (1958), who thought abnormal fat absorption might result from mitochondria breaking down to form the pigment.

There are many unanswered questions about this pigment. Why does it develop ? Is it the result of some nutritional defect ? What determines its maximal localization in jejunal muscle fibres ? It may represent the combined result of disturbed local conditions and a metabolic abnormality, but more must first be known about the details of lipochrome metabolism.

Summary

Pigment granules in fibres of the muscularis propria of the small intestine are described. These have been seen in a variety of diseases, having in common some abnormality of the gastro-intestinal tract.

About half the cases are associated with steatorrhoea. Three cases of jejunal diverticulosis were among the eight cases recorded here.

The staining reactions of the pigment suggest that it is a lipofuscin. Unlike similar pigment in other organs, age is not a primary factor in its development.

The pigment is thought to result from some metabolic abnormality possibly related to defective absorption.

I thank Dr. R. A. B. Drury for encouragement and help, and Dr. F. Avery Jones for clinical details.

REFERENCES

Adlersberg, D., and Schein, J. (1947). *J. Amer. med. Ass.*, **134**, 1459.
Ansanelli, V., and Lane, N. (1957). *Ann. Surg.*, **146**, 117.
Endicott, K. M., and Lillie, R D. (1944). *Amer. J. Path.*, **20**, 149.
Gresham, G. A., Cruickshank, J. G., and Valentine, J. C. (1958). *Nature (Lond.)*, **181**, 538.
Himes, H. W., and Adlersberg, D. (1957). *J. Mt Sinai Hosp.*, **24**, 251.
Hooper, C. W., and Whipple, G. H. (1917). *Amer. J. Physiol.*, **43**, 275.
Lillie, R. D., Ashburn, L. L., Sebrell, W. H., Daft, F. S., and Lowry, J. V. (1942). *Publ. Hlth Rep. (Wash.)*, **57**, 502.
Martin, A. J. P., and Moore, T. (1939). *J. Hyg. (Lond.)*, **39**, 643.
Nachtnebel, E. (1933). *Amer. J. Path.*, **9**, 261.
Pappenheimer, A. M., and Victor, J. (1946). Ibid., **22**, 395.
Paulley, J. W. (1954). *Brit. med. J.*, **2**, 1318.
Pearse, A. G. E. (1953). *Histochemistry, Theoretical and Applied.* Churchill, London.
Richards, W C. D. (1959). *Lancet*, **1**, 683.
Schwartz, M., and Jarnum, S. (1959). Ibid., **1**, 327.
Shiner, M. (1957). *Gastroenterology*, **33**, 64.
—— (1959). *Proc. roy. Soc. Med.*, **52**, 10.
Stewart, M. J., and Hickman, E. M. (1931). *J. Path. Bact.*, **34**, 61
Tverdy, G., Froehlich, A. L., and Fierens, B. (1949). *Acta gastro-ent. belg.*, **12**, 221.
Whipple, G. H., and Hooper, C. W. (1917). *Amer. J. Physiol.*, **43**, 258.

Medical Memoranda

Fatal Diphtheria in the Fully Immunized Child

Below is described a fatal case of diphtheria in a girl who had been fully immunized in infancy and had been given a booster dose at the age of 5.

CASE REPORT

A girl aged 8½ years complained of sore throat on November 14, 1958. Two days later she appeared listless and refused to eat ; the next day she developed stridor and was admitted to the infectious diseases unit of the Royal Free Hospital.

She had contracted measles, mumps, chicken-pox, and whooping-cough in infancy, and had been treated in a children's hospital for nephrosis but had fully recovered in 1955. In 1950 she had been given two injections of A.P.T., each containing 0.5 ml., separated by an interval of four weeks, and a booster dose of 1 ml. of T.A.F. in 1956.

On admission she was gravely ill and cyanosed, with obstructed respiration. The temperature was 100.8° F. (38.2° C.), pulse rate 152 a minute, and blood-pressure 90/60. A grey, adherent membrane covered both tonsils, extending over both anterior pillars of the fauces, soft palate, and uvula. The tongue was furred and the breath fetid. Glands in both sides of the neck were enlarged, with marked periadenitis, giving rise to a characteristic " bull-neck " appearance. A diagnosis of laryngo-tonsillo-pharyngeal diphtheria with laryngeal obstruction was made.

Emergency tracheotomy was performed and 96,000 units of A.D.S. given (80,000 units intravenously). Erythromycin was administered orally, 250 mg. every six hours, and the patient was placed in an oxygen tent.

Investigations.—Hb, 15.5 g./100 ml. (105%) ; W.B.C., 28,000 per c.mm. (90% polymorphs). The urine contained albumin + ; no red blood cells, casts, or organisms were