products of the cells. It is a gelatinous substance now called pseudo-mucin. Often the walls of adjacent loculi rupture and allow neighbouring cavities to communicate, and in this way large chambers form. It is not uncommon for a loculus near the periphery of the tumour to burst and allow the contents to escape into the belly. In some of the cases the amount of pseudo-mucin that collects in the belly is almost beyond belief.

A spinster, aged 54, was under my care in 1899 on account of an enlargement of the belly. The physical signs suggested an accumulation of fluid. The pressure was so great as to produce a hernial protrusion as big as a bantam's egg at the navel, and a similar one over the left femoral ring. A tumour could be felt in the pelvis. I removed three gallons of mucin and a mucigenous tumour of the ovary equal in size to a coco-nut. There was a rent in its capsule opening up three loculi, and through this rent the pseudo-mucin secreted by the mucous membrane lining the loculi escaped into the belly. The tumour was easily removed and the patient reported herself in good health five years after the operation.

Un Chiffonnier.

Many similar cases have been under my care and observation, but all do not end in this simple way. Occasionally, when a mucigenous tumour bursts, clumps of cells escape from the walls and settle on the peritoneum and act as grafts, and become independent tumours, discharging pseudo-mucin, which helps to increase the general mass. In some women hundreds of these pathological glands grow on the serous membrane, and the amount furnished in this way, after the primary tumour has been removed, is so great that it is necessary to open the abdomen annually for the removal of the pseudo-mucin. In removing this material care should be taken to protect the edges of the abdominal incision; it occasionally happens that the epithelial elements in the pseudo-mucin accidentally implanted will grow in the scar and form independent tumours. I have seen them as large as ripe gooseberries.

Surgeons are familiar with these remarkable tumours, concerning which the following facts may be stated: It is not uncommon to find in a woman one ovary occupied with a dermoid and the other converted into a mucigenous cyst. It is not rare to find an ovary transformed into a bilobed tumour one lobe of which is a typical dermoid and the other mucigenous. The inner walls of isolated cavities are often covered with cylindrical epithelium loaded with mucin and indistinguishable from the large cells found on the surface and recesses of the rectal polypi so common in children. Mucigenous tumours are often so large that it is only by chance the embryoma is detected. Quite by chance I saw one on the cut surface of a huge tumour. The embryoma presented as a patch of skin, less than 2 cm. square, bedecked with a tuft of delicate lanugo (Fig. 8).

I have studied the histology of these tumours in season and out of season, and often asked myself the question, Why is the intestinal tract rarely demonstrable in the ovarian embryoma? Gradually I have realized that the mucin (or pseudo-mucin) of these tumours is produced by the gastro-intestinal epithelium of the embryoma, and this, the active agent in the production of mucin, is masked by the accumulated products of its own activity.

The matter may be briefly expressed in this way: In the common kind of ovarian embryoma the cutaneous elements are conspicuous; the products resulting from the activity of the skin preponderate and make up the bulk of the tumour mass. In mucigenous ovarian tumours the so-called "colloid stuff" is furnished by the gastro-intestinal epithelium of the embryoma.

In dermoid tumours skin prevails.

In mucigenous tumours mucous membrane prevails.

In France the man who picks up rubbish in the streets and collects it in the *hotte* on his back is called a chiffonnier. The membranes of a uterine foetus, or the sac of an ovarian embryoma, serve to remind us of the *hotte* of the chiffonnier. The simile helps to illustrate the thesis set out in the beginning of this lecture: *Many tumours become manifest by the accumulation of the products of their own activity.*

LITERATURE.

- Eiselsberg: *Arch. f. klin. Chir.*, 1894, xlviii, 489.
Hédon: *Arch. de Physiologie*, 1892.
Minkowski: *Berl. klin. Wochenschr.*, 1892, 90.
Penfield, W. G.: Cranial and Intracranial Endotheliomata—Hemicraniosis, *Surg., Gyn., and Obstet.*, 1923, xxxvi, 657, with bibliography.
Shattock, C. E.: *Brit. Journ. of Surgery*, 1923, x, 39.
Spiller, W. G.: Hemicraniosis, *Journ. Amer. Med. Assoc.*, 1907, xlix, 2059.
Stokes, W.: *Trans. Acad. of Med. in Ireland*, 1884, ii, 452.

ARSENICAL PIGMENTATION OF THE MOUTH AND SKIN.

BY

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PIGMENTATION of the skin, varying in depth of colour from a light mottled grey to black-brown, and in extent from a small area to the entire surface of the body, is now well known as one of the occasional effects of the ingestion of arsenic in repeated small doses. It has occurred also very exceptionally and in mild degree after a single large dose.¹ The most detailed account of it has been given by Nielsen,² who in the course of his article makes two statements which have also been made by many other writers, either on his authority or their own. He says:

"A deposit of pigment in the mucous membrane of the mouth seems never to have been seen"; and

"A far more trustworthy symptom, which will serve for the diagnosis between arsenical melanosis and argyria and Addison's disease, is the fact pointed out by several writers that in arsenical melanosis the visible mucous membrane is never pigmented. It is true one case has been reported,²⁰ in which the bulbus oculi had been affected by pigmentation, but no case apparently where the mucous membrane of the mouth had been so affected."

I have, however, now met with two cases in which not only was the skin deeply pigmented, but the mucous membrane of the mouth shared markedly in the discoloration. One of these I reported in 1921.³ It was the case of a woman, aged 49, who had taken liquor arsenicalis daily for six years, and in that time had swallowed about 32,850 minims, equal to 298 grains (19.3 grams), arsenious acid. When I first saw her she had very extensive pigmentation of the skin, and keratosis of the palms and soles. The mucous membrane of the mouth and tongue had a bluish dark tint all over, and on the inner surface of the lower lip there was an irregular deep blue-black patch about the size of a sixpenny piece. She also had cirrhosis of the liver and ascites, but no neuritis.

The second case was that of a man, aged 57, suffering from pernicious anaemia, who developed marked pigmen-

tation of the skin and mouth while under my own observation and treatment in hospital.

When admitted he was extremely pallid, apathetic, and feeble; the red blood corpuscles numbered 800,000 per c.mm., and the haemoglobin was 20 per cent. He had taken no arsenic previously and was put on 10 minims liquor arsenicalis three times daily, this dose being continued for eighty days. By the end of that time the red corpuscles had risen to 2,400,000 and the haemoglobin to 41 per cent., but the arsenic had then to be discontinued as it was beginning to cause neuritis, evidenced by disappearance of his knee-jerks and tenderness of the posterior tibial nerves. He had taken 2,400 minims of Fowler's solution, equal to 21.8 grains (1.4 grams) arsenious acid. After he had been taking the arsenic for about one month it was evident that his skin was becoming pigmented. The pigmentation began, as it usually does, on the lower abdomen towards the flanks, but it spread and deepened very rapidly, until at the end of the eighty days the whole body was more or less discoloured. The lower abdomen and back, hips, and upper thighs were then of a black-brown colour, the rest of the trunk was of a bronze hue showing different tints and variegated with numerous small round white unpigmented spots, the face was light brown, and the arms and legs showed a mottled mixture of various shades of yellow and brown. The lines on the palms were picked out in a deeper brown than the surrounding skin. There was no extreme keratosis, but the epidermis of the hands and round about the knees was thick, reddened, and coarse, and showed a good deal of branny desquamation. About six weeks after beginning the arsenic several dark bluish patches appeared on the inner surface of the lower lip and at both angles of the mouth, the inner surface of the cheeks took on a uniform bluish colour with several deeper patches here and there, and there was one very marked brown area on the hard palate. When pressure was made with the fingers round about the patches on the lip and cheeks so as to render the area anaemic, their blue-black colour changed to a light brown, showing that the peculiar bluish-black tint is due to the purple colour of the capillary blood modifying the brown of the pigment present in the epithelial cells.

As regards the pigmentation of the skin and mouth I cannot say that the appearances differed in any way from certain cases of Addison's disease. There was, however, at parts, a distinct tendency to coarsening, hyperaemia, and branny desquamation of the skin, not seen in the latter. The colours in the mouth deepened considerably as he went on taking more arsenic. Within one week after stopping it there was a visible lessening of coloration both in the skin and mouth, and in a fortnight the change was more decided, and accompanied by fine scaly desquamation at the more deeply discoloured areas of the skin. In a month the face was nearly normal in colour, the forearms and legs were of a yellowish tint, and elsewhere the pigmentation had lessened. The brown patch on the palate had disappeared entirely, but the blue-black spots on the lips could still be easily made out. He then left hospital at his own request and died two months later of pernicious anaemia. By this time his skin had again become pallid, and there was little or no trace of pigmentation.

During the prolonged treatment with arsenic of cases of chorea, pernicious anaemia, lymphadenoma, psoriasis, and other chronic diseases, pigmentation of the skin and keratosis are not infrequently produced, but their occurrence must be considered as relatively very rare in proportion to the large number of cases which are so treated without any untoward effects. It is notorious that arsenic causes these and other pathological lesions much more rapidly and after a much smaller quantity in some persons than in others.³ Thus, pigmentation, keratosis, and neuritis may appear in a few weeks or months, all together or singly, or may not appear at all even after years of arsenic administration. The reason of this variation in action is unknown, and for the present it has to be put down to individual differences or idiosyncrasy.

The skin coloration fades with very varying rapidity, sometimes in a few weeks, sometimes only after months, or in two or three years, and Cheadle⁴ has recorded an instance of its being present after nine years and presumably permanently. In my experience it almost invariably disappears fairly rapidly, and has no deleterious influence on the general health. This is also true of keratosis, although it also may be very persistent, and arsenic cancer may result from prolonged irritation of the skin by the drug.⁵ On the other hand neuritis, which is equally capricious in its incidence, is very tedious and difficult to cure, and its possible occurrence should always be carefully watched for and avoided. It may prove permanent and even fatal in extreme cases.³

It is difficult to determine exactly when or by whom pigmentation of the skin was first noticed as a result of the therapeutical administration of arsenic. Arsenious acid, realgar, and orpiment have been used continuously

from the earliest medical times, and their acute poisonous effects have long been familiar, but knowledge regarding the symptoms of chronic poisoning has dawned much more slowly.

Arsenical paralysis is said to have been first recorded in the thirteenth century, and at infrequent intervals afterwards till 1857,⁶ when it was more particularly described by Leroy,⁷ and since then by very many others. In the eighteenth century, when various preparations of arsenic were widely and successfully used in the treatment of agues, it was known that they might give rise to paralysis and dermatitis, but there is no record of pigmentation. Thickening of the skin was noted by Hunt,⁸ and later by Wilson (in 1873),⁹ but it was only after 1888, when keratosis of the soles and palms and other parts was first definitely drawn attention to by Jonathan Hutchinson,⁵ that this very striking effect of the administration of arsenic came to be generally recognized. Its employment in chorea is also comparatively modern. Harles (1811)¹⁰ merely mentions it without comment of any kind, and Martin,¹¹ Salter,¹² and Gregory¹³ seem to be the earliest writers who published accounts of cases successfully treated with it. Later Begbie¹⁴ and Pereira¹⁵ spoke very highly of its value from their own experience. In 1877 Byrom Bramwell first advocated its use in pernicious anaemia.¹⁶

Arsenic was first employed accurately and systematically in skin diseases by Dr. Thomas Girdlestone¹⁷ of Yarmouth in 1806, and in 1847 Hunt,⁸ and later Devergie,¹⁸ in their treatises on diseases of the skin, describe brown and grey discoloration as if this were a recognized and not uncommon incident during its administration. Hunt describes the skin as having a "dirt-brown, dingy, unwashed appearance," and Devergie uses the terms "iron-grey" and "brown." Veiel (1860)¹⁹ says it occurs "not seldom." Since then it has been described in great detail by many writers. The colour may be mottled light or dark grey, the mottling being due to irregularities in the depth of pigmentation, or it may be in all shades of brown—pale, yellowish, coffee, bronze, dull coppery, or almost black. It is never equally deep over the whole surface, or even in the same area of the body, and the tint is often modified at places by hyperaemia in underlying patches of the corium. Small roundish spots of unpigmented, or more deeply or more slightly pigmented, skin are always present, and this with the differences in colour-shades gives an impression of mottling. Warty growths are often present. On the rosa of the lips and mouth the brown deposit is modified to a dark bluish colour by the underlying tissues and blood, as has been previously mentioned, other instances of the same kind being the more familiar "blue line" of lead poisoning, and the bluish colour of the lips in dark-skinned races.

Erasmus Wilson²⁰ in 1868 gave an account of the nature of the pigment, which he describes as the ordinary melanin of the skin, and relates a case in which the eyeball presented a "dark tinge" in addition to deep cutaneous discoloration. But so far as I have been able to ascertain the two foregoing cases are the only instances in which pigmentation of the mucous membrane of the mouth has been recorded.

More careful examination of cases in which the skin is deeply pigmented would probably show, however, that the mouth is also not infrequently involved.

REFERENCES.

- ¹ Moreira: *Brit. Journ. Dermatol.*, vii, 378, 1895. ² Nielsen: *Melanosis and Keratosis Arsenicalis*, New Sydenham Soc., 1900. ³ Stockman: *Edin. Med. Journ.*, July, 1921. ⁴ Cheadle: *Practitioner*, xxxvi, 90, 1886. ⁵ Semon: *BRITISH MEDICAL JOURNAL*, 1922, ii, 975. Hutchinson: *Trans. Path. Soc. London*, xxxix, 352, 1888; New Sydenham Society's *Atlas*. ⁶ Alexander: *Lähmungen nach Arsenik-Vergiftung*, 1889. ⁷ Leroy: *Gaz. hebdom. de Méd.*, 1857, 141. ⁸ Hunt: *Practical Observations on the Pathology and Treatment of Certain Diseases of the Skin*, 1847; *Diseases of the Skin*, ninth edition, 1871. ⁹ Wilson: *Lectures on Dermatology*, 1873, 151. ¹⁰ Harles: *De Arsenici Usu in Medicina*, p. 207, Nürnberg, 1811. ¹¹ Martin: *Med.-Chir. Trans.*, iv, 45, 1813. ¹² Salter: *Ibid.*, x, 218, 1819. ¹³ Gregory: *Ibid.*, xi, 299, 1821. ¹⁴ Begbie: *Monthly Journ. Med. Sci.*, i, 740, 1847. ¹⁵ Pereira: *Materia Medica and Therap.*, i, 714, 1854. ¹⁶ Bramwell: *Edin. Med. Journ.*, November, 1877. ¹⁷ Girdlestone: *London Med. and Physical Journ.*, 1806. ¹⁸ Devergie: *Traité des Maladies de la peau*, 1854, p. 106; *Bull. gén. de Thérap.*, 1869, 49. ¹⁹ Veiel: *Schmidt's Jahrbücher*, 1860, 108, p. 162. ²⁰ Wilson: *Journ. of Cutaneous Med.*, i, 354, 1868.