Primary melanocarcinoma of the esophagus

D. L. C. Bingham, F.R.C.S., L. C. Chadsey, M.D., S. Ramchand, M.B., B.S. and P. J. Doris, M.D., *Kingston, Ont.*

Primary malignant melanoma of the esophagus is exceedingly rare. Since the first case was reported by Bauer[1] in 1906, only 29 more have been recorded in the world literature. The 31st case, and the first to be reported in Canada, is described in this communication. It has encouraged us to review the clinical features, pathology and management of the disease.

C.S., a 53-year-old white man, was admitted to the Kingston General Hospital on January 6, 1970. His chief complaints were:

(1) Increasing difficulty for more than two months in the swallowing of solid food, such as meats. Liquids could still easily be swallowed.

(2) A feeling of fullness and discomfort in the chest after eating and, especially and increasingly in the previous four weeks, anorexia and regurgitation of meals.

(3) Increasing fatigability, so that his work as a carpenter had become burdensome.

(4) Loss of weight of 45 lbs. in the previous five months.

Before the onset of these symptoms the patient's health had always been excellent; his only previous illness had been an attack of tonsillitis at the age of 30, for which he had had a tonsillectomy. There was no family history of cancer, heart disease or diabetes.

The patient was a robust, healthy-looking man. Examination of each of the systems was normal. His blood pressure was 118/80. No lymph nodes were palpable in the neck or axillae; the abdomen was normal and no cutaneous nevi or pigmented areas were present anywhere on the skin, in the mouth or in the rectum. Ophthalmoscopic examination disclosed several pigmented areas in the left fundus, without associated induration, which were considered to be evidence of healed retinitis.

Of numerous laboratory examinations only the leukocyte count was slightly abnormal at 14,000 per c.mm. and the sedimentation rate was elevated to 69 mm. in the first hour. There was no occult blood in the stool. Serum proteins and the electrophoretic strip were normal. The electrocardiogram revealed normal sinus rhythm with minor, not diagnostic, S-T changes.

On January 8, routine chest x-ray was normal, but a barium meal revealed a large lobulated tumour in the distal esophagus measuring 10 cm. in length and 4 cm. in width in its widest diameter. The tumour seemed to arise from the anterior and left lateral walls of the esophagus; the right lateral and posterior esophageal walls at the same levels were not involved. The tumour had caused considerable proximal dilatation of the esophagus, but the area distal to the tumour seemed to be normal (Figs. 1 and 2).

The stomach could not be adequately visualized as it was impossible for sufficient barium to pass the obstructing tumour in the esophagus.

It was concluded that a large tumour occupied the distal esophagus and that although the appearances were unusual for a squamous cell carcinoma, this was the most probable diagnosis. Among other diagnoses considered were polypoid adenocarcinoma or a leiomyosarcoma.

Esophagoscopy on January 9 revealed a large deeply pigmented polypoid tumour occupying and obstructing the distal esophagus with a number of large veins coursing over it. The tumour was not biopsied as its complete removal was clearly indicated.

Preoperative preparation consisted of a semi-fluid, high-protein diet, systematic evacuation of the colon, and the administration of 1 g. neomycin four times a day for four days.

On January 13, the chest was opened through the bed of the left sixth rib. The inferior pulmonary ligament was divided and the esophagus was exposed by opening the mediastinal pleura from the diaphragm to the aortic arch. Minimal edema fluid was present in the loose areolar tissue overlying the lower third of the esophagus. Two pigmented lymph nodes lying on its anterior aspect were removed and sent for frozen-section examination. These were reported to be anthracotic and free from tumour.

The esophagus was then resected from the esophagogastric junction to just behind the aortic arch and with it were also removed all excisable peri-esophageal lymph nodes and areolar tissue.

The specimen was then sent for frozen-section examination, to determine the nature of the tumour and whether the esophageal and gastric resection lines were

From the Departments of Surgery and Pathology, Queen's University, and Kingston General Hospital, Kingston, Ontario.
Reprint requests to: Dr. D. L. C. Bingham, The Professional Building, Suite 203, 11 Princess Street, Kingston, Ontario.

free of tumour. A frozen-section diagnosis of malignant melanoma was made and it was also reported that the resection lines were free of tumour.

The chest was then temporarily closed and a left paramedian incision was made from the left costal margin to below the umbilicus. Exploration of the abdomen revealed no metastases. Lymph nodes around the celiac axis and along the curvatures of the stomach were normal, and no deposits could be seen or felt in the liver. Examination of the colon showed that the ascending branch of the left colic artery and its accompanying veins were large and provided a rich blood supply to and adequate drainage from the left half of the tranverse colon and proximal descending colon.

Consequently, after the omentum had been detached from these parts of the colon, the bowel and marginal vessels were divided just to the right of the middle of the transverse colon and also in the middle of the descending colon. Continuity between proximal right colon and distal left colon was then re-established by anastomosing the right half of the transverse colon to the distal descending colon. The left half of the transverse colon and proximal half of the descending colon thus became totally dependent for their blood supply upon the left colic artery and its ascending branch. This seemed to be adequate and consequently the proximal end of this loop of colon was brought up into the posterior mediastinum posterior to the stomach and through the esophageal hiatus, which was gently dilated to accommodate it comfortably. An anastomosis was then performed between the proximal esophagus and colon, at the level of the arch of the aorta, using two layers of 00 interrupted silk stitches.

The colonic esophageal replacement was then secured in the esophageal bed in the posterior mediastinum under slight longitudinal tension to avoid subsequent redundancy; the hiatus was also carefully closed around it with 000 silk stitches. The chest was then closed in the usual manner with underwater drainage.

The abdomen was then re-entered and the distal extremity of colonic esophageal replacement was anastomosed to the posterior surface of the stomach at about the junction of its proximal one-third with the distal two-thirds, thus ensuring that there would be an intra-abdominal portion of colon of about 4″ in length. Finally, a Heineke-Mikulicz pyloroplasty, using the Weinberg technique, was constructed and the abdomen was closed in layers in the usual way.

A Levin tube was passed through the new esophagus into the stomach, and gastric contents were continuously aspirated for six days. From the first postoperative day the patient was given lemon-flavoured ice chips to suck, and water by mouth was permitted on the fourth day. The chest drain was removed on the third postoperative day. Sustagen, 200 ml., was given orally every six hours from the fifth postoperative day, and on the seventh postoperative day a soft diet was allowed.

On the tenth postoperative day the esophagus, stomach and duodenum were examined by cinefluorography and spot films were taken. These examinations revealed normal peristalsis in the remaining upper esophagus. No peristalsis was noted in the colonic segment that replaced the lower esophagus but, in the upright position, barium passed freely through it into the stomach, with only slight residual retention above the gastrocolonic anastomosis. In the supine and semiprone positions there was more barium retention in the intra-abdominal portion of the colonic esophageal replacement but no reflux could be demonstrated in either the upright or supine positions.

The patient was discharged from hospital on January 24, 1970, the eleventh postoperative day.

When examined April 8, 1970, he had regained 18 lbs. in weight, was able to eat and drink normally, had no symptoms of reflux of gastric contents into the esophagus and had returned to work. Unhappily, a radiograph of the chest revealed a metastasis in the right lung root and he eventually died on December 17, 1970, with widespread metastases.

Pathological findings: The fixed specimen consisted of a segment of esophagus measuring 8 cm. in length and 7 cm. in circumference. The external surface was unremarkable but upon it was an ovoid, firm lymph node, 0.8 cm. in its longest diameter. Five centimetres from the proximal resected margin and 2 cm. from the distal resected margin was a large, firm, pedunculated polypoid tumour. It had a coarsely lobulated superficial surface with many irregular areas of black pigmentation (Fig. 3). The tumour had a well-defined stalk, almost a mucosal fold, which measured 1 cm. in diameter. When the tumour was sectioned the cut surface was pinkish-white with irregular deeply pigmented areas. The adjacent mucosa and the rest of the esophagus showed no areas of pigmentation. Two para-esophageal lymph nodes submitted for frozen section during operation showed no evidence of invasion by malignant cells.

Microscopic description: The tumour was very cellular and was composed of clumps, clusters and cords of neoplastic cells of varying morphology. Many of the clusters were separated from each other by fine strands of connective tissue and reticulin, and had a tendency to form an alveolar pattern. In the less differentiated portions of the tumour the cells showed little or no tendency to form an alveolar arrangement.

The size and shape of these neoplastic cells varied very greatly, from round or oval to markedly elongated spindle and fusiform shapes (Figs. 4 and 5). The nuclei were round, oval or fusiform with a diffuse reticular chromatin pattern. Giant

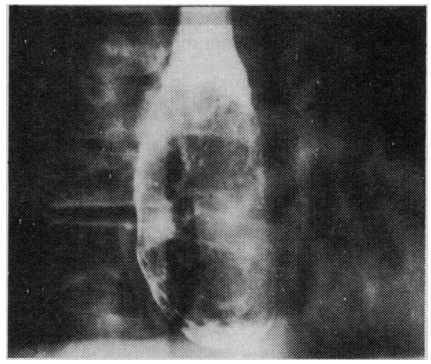

FIG. 1—Anteroposterior view of the lower third of the esophagus showing the extent of the tumour and its characteristic lobulation.

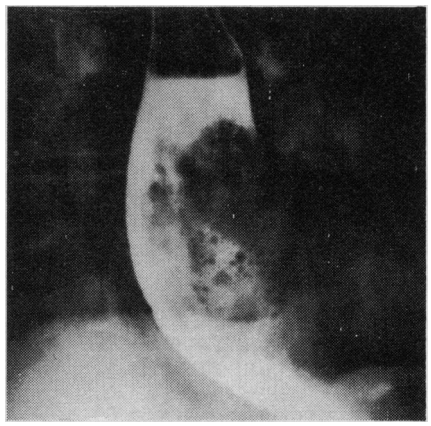

FIG. 2—The right oblique view of the lower third of the esophagus, which suggests that the tumour does not encircle the esophagus but is attached to and originates from its left side.

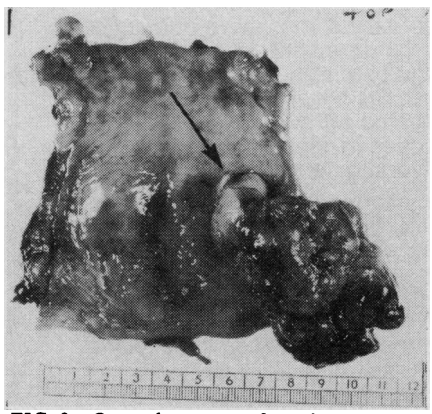

FIG. 3—Opened segment of esophagus showing a large, pedunculated, polypoid tumour with lobulation and areas of pigmentation. Attachment to mucosa indicated by arrow.

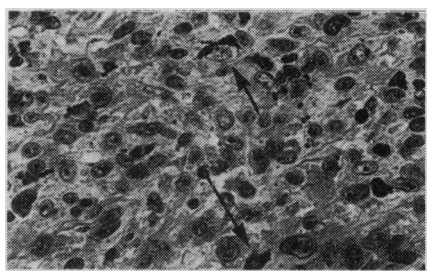

FIG. 4—Cluster of oval to round neoplastic cells showing moderate variation in nuclear size and shape. Note prominent nucleoli. Scattered cells contain pigment granules (arrows). (Hematoxylin, phloxine and saffron, x 500.)

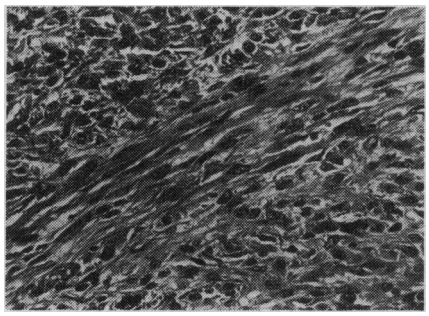

FIG. 5—Tumour cells of elongated spindle and fusiform shapes interspersed with others similar to those illustrated in Fig. 2, but at a lower magnification. (Hematoxylin, phloxine and saffron, x 312.)

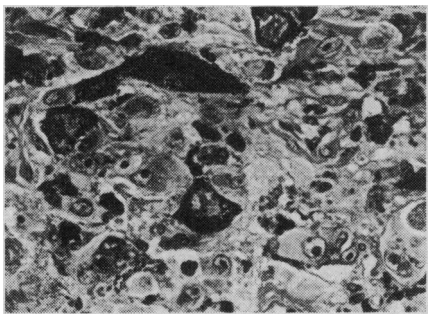

FIG. 6—Aggregate of tumour cells with varying amounts of melanin in the form of fine and coarse granules. Two cells are obviously overloaded with pigment obscuring nuclear detail. Note variation in nuclear and cellular configuration as well as prominent nucleoli. (Hematoxylin, phloxine and saffron, x 500.)

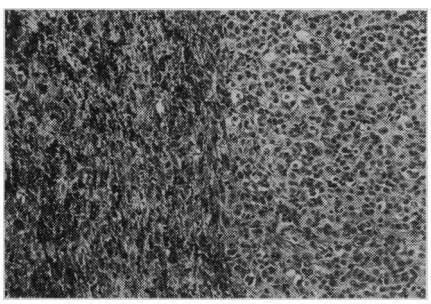

FIG. 7—Variable appearance of tumour cells is evident. Adjoining pigmented and non-pigmented tumour cells occurring in sheets. (Hematoxylin, phloxine and saffron, x 125.)

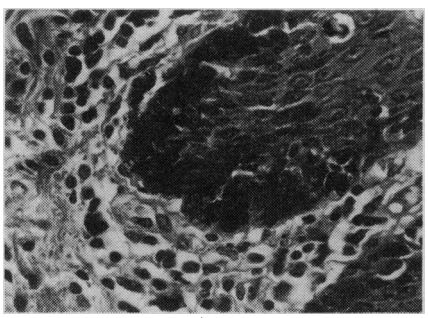

FIG. 8—Junctional change. Basal cells of uninvolved but adjacent squamous epithelium showing melanin pigmentation. Note loss of cohesion and suggestive "dropping off" of epithelial cells into subepithelial tissues. (Hematoxylin, phloxine and saffron, x 500.)

nuclei were common and nucleoli prominent. Mitosis was not a striking feature and abnormal mitotic figures were not seen.

The cytoplasm of the tumour cells varied from narrow, faintly basophilic rims to a vast abundance with cytoplasmic processes. Focal aggregates and clusters of neoplastic cells contained fine and coarse granules of a brown-black pigment which varied in amount in individual cells, some having an overloaded appearance (Fig. 6). Not all cells, however, contained pigment, and large areas of pigmented tumour cells were interspersed between non-pigmented ones (Fig. 7). This pigment gave a positive reaction with Fontana's silver stains[40] and Lillie's ferrous iron technique[41] and was bleached with potassium permanganate and hydrogen peroxide.[42] Perls' reaction for iron was negative. A section of the fresh tumour gave a positive DOPA reaction.[43]

The adjacent uninvolved esophagus was carefully studied for "junctional change". The cells of the basal and lower layers of the epithelium showed loss of cohesion and slightly enlarged and hyperchromatic nuclei, and contained pigment granules similar to those seen in the tumour cells (Fig. 8). Scattered darkly pigmented cells were also present in the lamina propria (Fig. 9). This change could be traced from uninvolved regions of the esophagus to frankly neoplastic areas.

Individual tumour cells as well as nests of tumour cells infiltrated the muscular layers of the esophagus. The resection margins and lymph nodes, however, were free of tumour.

Discussion

Clinical aspects

During the last 64 years 31 cases of primary malignant melanoma of the esophagus have been reported. The youngest patient, and the only child, was a boy aged 7; the oldest, a woman, was 82. Apart from the former, only one other patient was under the age of 40, a woman of 38. The average age of the 19 males was 57 years and of the 12 females, 60. As far as can be determined from the case reports, all, except one woman aged 48 who was

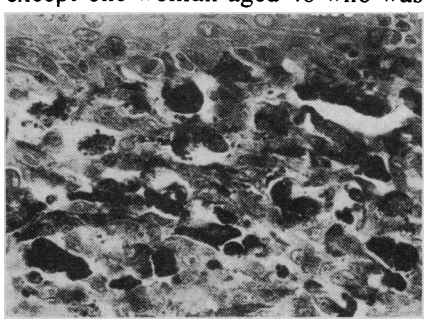

FIG. 9—Active junctional change. Another area of uninvolved but adjacent squamous epithelium showing advanced changes. Note deep pigmentation and loosening of basal cells with pigmented cells in subepithelial tissues. (Hematoxylin, phloxine and saffron, x 500.)

operated upon by Pomeranz and Garlock[10] in September 1953 and was alive and well six and a half years later,[24] died from their disease within two and a half years of its discovery and treatment, and nearly half of them died within six months. Primary malignant melanoma of the esophagus is therefore no less fatal than malignant melanoma originating in any other part of the body.

The clinical features of the reported cases were increasing esophageal obstruction, with difficulty in swallowing solid foods, and a feeling of fullness and discomfort or even pain in the chest after eating.

Loss of weight was present in every case. It varied from 3 to 45 lbs. and, as is usual in patients with esophageal obstruction, was proportional to the duration of symptoms. Steatorrhea was a frequent complaint and increasing fatigability and weakness were usual.

Physical signs of the disease, apart from those of recent weight loss, were generally absent. Only one patient had clinical evidence of spread to lymph nodes in the neck, and in only two patients was blood present in the stool.

Routine blood studies, blood chemistry and urinalysis were normal in all cases.

Barium meal x-ray examinations were carried out in 27 cases. A filling defect was found in 24 cases, but in two patients the lesion was not detected, and in one case the defect in the esophagus was discovered only at the third examination. In one case the lesion was considered to be a benign tumour. In all but three cases the tumour was bulky and polypoid. It did not completely encircle the esophagus but seemed to arise from a stalk or pedicle (a feature which may be of value in the differential diagnosis between melanocarcinoma and the much more common squamous cell carcinoma of the esophagus).

Esophagoscopy usually revealed a bulky, polypoid, irregularly pigmented and obstructing esophageal tumour, the nature of which was disclosed by biopsy. There is no report of excessive bleeding from the tumour after biopsy.

In the recorded cases treatment was symptomatic in eight; one received radiation without discernible benefits; one[15] discharged himself from hospitals and died two years later at home; two received no treatment, the disease being diagnosed at

postmortem examination; and in 20, esophageal resection was performed. In 19 cases esophagogastric continuity was re-established by esophagogastrostomy. The case we report is the first to have had a mobilized segment of colon interposed between the proximal esophageal remnant and the stomach distally. As has already been noted, only one patient has survived for more than three years, a melancholy tribute to the aggressiveness of the disease.

Pathological aspects

The occurrence of primary melanocarcinoma arising in the esophagus has been questioned by many investigators. For example, Stout and Lattes[30] in 1957 stated "we do not wish to deny that malignant melanomas can be primary in the esophagus; we simply regard the publicized evidence as unconvincing." The most serious objection to acceptance was that until 1963 melanoblasts had not been convincingly demonstrated in the esophagus. In 1963, however, de la Pava *et al.*[31] reported that in four out of 100 esophagi studied, typical melanoblasts with melanin granules and dendrites were found in the basal layer of the esophageal epithelium. These were present in the upper third of the esophagus in two cases and in the middle third in two. The authors speculated that these melanoblasts had migrated to the esophagus from the neural crest as they do to the skin.

Melanoblasts are normally present in the basal layer of the oral mucous membrane and melanin pigmentation of the mouth may occur in a variety of clinical conditions, as well as physiologically among Negroes and many of the Caucasian races.[32] Malignant melanoma of the mouth and pharynx is, however, also rare and up to 1958 Chaudhrey, Hampel and Gorlin[33] were able to collect only 105 such cases from the world literature.

It is likewise curious that secondary malignant melanoma of the esophagus is also very rare, only three cases having been reported up to 1962.[34-36] In addition other metastatic neoplasms simulating primary esophageal carcinoma are also unusual, only 42 cases having been reported up to 1942.[37]

The presence of junctional changes in the overlying or adjacent epithelium was considered by Allen[38] to be unequivocal evidence of a primary malignant melanoma and "the absence of junctional changes over a dermal melanomatous deposit is strong evidence that the melanoma is metastatic at the site in question". In a later paper Allen and Spitz,[39] after a review of 934 cases of melanoma, broadened the concept of junctional change as an essential criterion of primacy to include visceral melanomas wherever they may arise. In the esophagus, however, some authors[14, 17, 29] believe that a rapidly growing and expanding tumour may destroy adjacent junctional change and that the absence of the latter is not conclusive evidence that the tumour is not primary at the site in question.

It appears to us that, ideally, a diagnosis of primary malignant melanoma of the esophagus should be based on the following criteria: (1) The tumour should have the characteristic structure and appearance of a melanoma and contain melanin. (2) It should arise from an area of junctional change in squamous epithelium. (3) The adjacent epithelium should show junctional changes with the presence of cells containing melanin.

In the present case there is little doubt that the lesion reported is a malignant melanoma. The histological features are characteristic of those reported for melanocarcinoma at other sites and there is substantial evidence that the tumour originated in the esophagus from the presence of active junctional changes or "pagetoid loosening"[13] of the germinal layers of the squamous epithelium, generally accepted criteria for the diagnosis of primary melanocarcinoma.

References:

1. BAUER EH: Ein Fall von primarum Melanom des Oesophagues. *Arb Pathol Anat Inst Tubingen* 5: 343-354, 1906
2. JOLIAT H: *Contribution à la pathologie de l'Oesophage,* Lausanne, E Frankfurter, 1907
3. MOERSCH HJ, BRODERS AC: Melano-opithelioma of the esophagus. *JAMA* 88: 1319-1320, 1927
4. VOSS E: Ein Fall von Melansarkom des Osophagus. *Z Pathol* 36: 353-362, 1928
5. JALESKI TC, WALDO PV: Primary melanotic sarcoma of the esophagus. *Am J Cancer* 24: 340-344, 1935
6. PUYO R, PORTMANN M: Mélano-carcinoma primitif de l'oesophage. *Rev Laryng Otol Rhinol (Bord)* 71: 178-183, 1950
7. BURNETT JM, ST. JOHN E: Primary melano-sarcoma of the esophagus. *Radiology* 57: 868-869, 1951
8. CHALMAGNE J: Un cas de cancer mélanique de l'oesophage. *Acta Oto-rhinolaryng Belg* 5: 76-79, 1951
9. FOWLER M, SUTHERLAND HD: Malignant melanoma of the oesophagus. *J Pathol* 64: 473-477, 1952
10. GARFINKLE JM, CAHAN WG: Primary melanocarcinoma of the esophagus; the first histologically proved case. *Cancer* 5: 921-926, 1952
11. CITTERIO L: Melanoblastoma dell'esofago. *Archivio di chirurgia del torace* 10: 289-297, 1953
12. BULLOCK WK, THOMPSEN HL, GREGORY G: Primary melanocarcinoma of the esophagus; the third histologically proved case. *Cancer* 6: 578-580, 1953
13. BOYD DP, MEISSNER WA, VELKOFF CL, et al: Primary melanocarcinoma of the esophagus; report of a case. *Cancer* 7: 266-270, 1954
14. ROBERTSON JW: Malignant melanoma of the esophagus, as one of multiple malignant tumors. *Gastroenterology* 27: 121-126, 1954
15. SIRSAT MV: Malignant melanoma of the esophagus; report of a case. *Indian J Med Sci* 9: 121-126, 1954
16. POMERANZ AA, GARLOCK JH: Primary melanocarcinoma of the esophagus. *Ann Surg* 142: 296-301, 1955
17. LORING WE, ZEPPA R: Melanocarcinoma of the esophagus. *J Thorac Surg* 32: 35-36, 1956
18. KEELEY JL, ROONEY JA, GUZANSKAS AC, et al: Primary malignant melanoma of the esophagus. *Surgery* 42: 607-614, 1957
19. NÈGRE E, GUIBERT H, CAZALIS C: Naevo-épithéliomes primitifs de l'oesophage. *J Chir* 76: 263-271, 1958
20. FLEMING PC, VAN DER MERWE SB: A case of primary malignant melanoma of the esophagus. *Br J Surg* 46: 121-123, 1958-59
21. FERRO FE, MILLER EW, MORNINGSTAR WA, et al: Primary melanoma of the esophagus. *Arch Surg* 76: 492-495, 1958
22. GUIBERT HL, ORIOL R: Primary melanomas of the oesophagus. *Rev Laryngol Otol Rhinol (Bord)* 81: 46-91, 1960
23. MINWALLA SP, PARRY WR: A case of primary malignant melanoma of the esophagus. *Br J Surg* 48: 461-462, 1960-61
24. SUEHS OW: Malignant melanoma of the esophagus. *Ann Otol* 70: 1140-1147, 1961
25. BARTSCH WM: Primary malignant melanoma of the esophagus. *Bruns Beitr Klin Chir* 202: 427-440, 1961
26. WAKEN JK, BULLOCK WK: Primary melanocarcinoma of the esophagus. *Am J Clin Pathol* 38: 415-421, 1962
27. SAKORNPANT P, BARLOW D, BEVAN CM: Two cases of primary malignant melanoma of the oesophagus. *Am J Clin Pathol* 53: 386-388, 1964
28. RAVEN R, DAWSON I: Malignant melanoma of the esophagus. *Br J Surg:* 51: 551-555, 1964
29. BASQUE GJ, BOLINE JE, HOLYOKE JB: Malignant melanoma of the esophagus: first reported case in a child. *Am J Clin Pathol* 53: 386-388, 1964
30. STOUT AP, LATTES R: *Tumors of the esophagus,* Washington, U.S. Armed Forces Inst Pathol, 1957, p 104
31. DE LA PAVA S, NIGOGOSYAN G, PICKREN JW, et al: Melanosis of the esophagus. *Cancer* 16: 48-52, 1963
32. ROBINS SL: *Textbook of Pathology,* Philadelphia, Saunders, 1964, p 426
33. CHAUDHREY AP, HAMPEL A, GORLIN RJ: Primary malignant melanoma of the oral cavity. *Cancer* 11: 923-928, 1958
34. SPIEGELBERG H: Ausgebreitete Melanosarcomatose als Metasase eines Tumors der Opticusscheide. *Virchows Arch Pathol Anat* 142: 553, 1895
35. RANIERI, M: Un caso non comune di mela-

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BOOK REVIEWS

Disorders of Carbohydrate Metabolism

A Symposium held at the Royal Society of Medicine in London, November 29-30, 1968. Edited by G. K. McGowan and G. Walters. 81 pp. Illust. British Medical Association, Tavistock Square, London, 1969. $3.75 (U.S. funds) paperbound.

This symposium was held in London, England in November 1969 and covered a wide range of disorders of carbohydrate metabolism. The discussants stressed that congenital disorders of carbohydrate metabolism were often missed in infancy. These conditions should be sought more diligently, especially in infants found to have an enlarged liver. It could be due, for instance, to glycogen storage disease, to galactosemia, or to hereditary fructose intolerance. There is a timely reminder that whereas Clinitest or Benedict's test detect all reducing substances in the urine, paper strip tests are specific for glucose.

Hormonal control of carbohydrate metabolism, disorders of fructose metabolism, hyperinsulinism, disorders of carbohydrate digestion and absorption and glycogen storage disease are among the subjects discussed. Diagnosis of diabetes mellitus by H. Keen and discussion of practical aspects of the investigation of disorders of carbohydrate metabolism by Vincent Marks are of immediate usefulness to practising physicians. The relationship between carbohydrates, fats and atherosclerosis discussed by Ian MacDonald is timely, and G. Neligan raises many practical points in his discussion of hypoglycemia in infancy and childhood. K. W. Taylor deals with the elusive problem of the pathogenesis of diabetes mellitus. In line with present thinking he considers it a multifactorial disease, and states that in most diabetics its etiology is completely unknown. A potent genetic element is admitted, but to this such factors as obesity, pregnancy and endocrine disorders have to be added. There is a strong likelihood that additional acquired factors may have a direct destructive effect on the beta cells themselves. Such factors may be toxic, autoimmune or perhaps viral, but this is very hard to prove.

In the paper by P. J. Randle the interest is centred on the possible controls of the various pathways of carbohydrate metabolism by one or two key enzymes which function as pacemakers. The possibility exists that enzymes which have both catalytic and regulatory activity may play a role in diabetes.

Insulin deficiency leads to insulin unresponsiveness of muscle which is similar to that caused by oxidation of fatty acids. It may be in fact due to accelerated triglyceride breakdown and fatty acid oxidation. Perhaps administration of inhibitors of fatty acid oxidation could reverse this abnormality of carbohydrate metabolism in diabetic muscle.

D. A. Pyke's discussion of diabetic ketosis and coma includes determinations of insulin levels and other laboratory findings during the acute stage from hperosmolar non-ketotic coma and after recovery. The cause of the comatose state in this condition is not fully understood as consciousness has been maintained in patients with a calculated plasma osmolarity of 376 m-osm/l. or nore. Nor is the cause of extreme hyperglycemia in some of these patients always obvious. Some circulating insulin has been demonstrated conclusively in his cases and it was striking how mild the diabetes could become after recovery from coma. Of the 16 cases treated, 15 survived and eight subsequently were controlled without insulin. One man was admitted in typical keto-acidotic coma with a plasma bicarbonate level of 2 mEq./l. nine months after recovery from hperosmolar coma without keto-acidosis.

This slender volume is crammed with stimulating information and should appeal not only to physicians treating metabolic diseases but also to pediatricians and internists.

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nosarcoma della cute con probabile metastasi all'esofago. *Gazzetta Degli Ospedali E Delle Cliniche* 62: 232-235, 1941

36. ROSEN IB: Secondary malignant melanoma of the esophagus and its treatment. *Can J Surg* 5: 442-446, 1962
37. SASSON L: Metastatic neoplasm of the esophagus simulating primary carcinoma. *JAMA* 174: 2075-2076, 1960
38. ALLEN AC: A reorientation on the histogenesis and clinical significance of cutaneous nevi and melanomas. *Cancer* 2: 28-56, 1949
39. ALLEN AC, SPITZ S: Malignant melanoma; a clinicopathological analysis of the criteria for diagnosis and prognosis. *Cancer* 6: 1-45, 1953

40a CULLING CFH: *Handbook of Histopathological Techniques*, London, Butterworth, 1963, p 254

40b Idem: Ibid, p 308

41. LILLIE RD: Ferrous ion uptake; a specific reaction of the melanins. *Arch Pathol* 64: 100-103, 1957
42. PEARSE AGE: *Histochemistry, Theoretical and Applied*, second ed, Boston, Little, Brown, 1960, p 920
43. BARKA T, ANDERSON PJ: *Histochemistry*, New York, Harper & Row, 1963, p 328