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Valda M. Craddock
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1

Introduction: the problem, incidence, etiology. A working hypothesis

Esophageal cancer is one of the most common cancers world-wide, having a higher global incidence than the much-studied cancer of the liver. When added to oral and pharyngeal cancers, which have a similar etiology, cancers of the upper alimentary tract form the most prevalent cancers world-wide (Parkin *et al.* 1988). The difference in rate between high and low incidence areas around the world is extreme, ranging from 0.4/100000 for women in the state of Utah, USA, to 170/100000 in the Gonbad region of Northern Iran. Even within any country, the geographical distribution of the cancer is often very sharply demarcated, exceptionally high-risk regions neighbouring onto districts with a much lower risk. At the French/Belgian and the Kenya/Uganda borders there is a sharp change in incidence at the political boundaries. Epidemiological studies carried out in these situations have very strongly implicated a variety of risk factors, notably alcohol consumption, deficiencies of certain micronutrients, consumption of food contaminated by mycotoxins, and a low consumption of fresh fruit and vegetables. None of these factors, however, has been shown to cause esophageal cancer in experimental animals.

Thousands of chemicals have been tested for carcinogenicity, but the only compounds found to be potent carcinogens for the esophagus in animal experiments are the nitrosamines. All species tested were found to be susceptible, from amphibia to primates, and there is no apparent reason why man should be excepted. Human exposure to *N*-nitroso compounds, either from intake in food or consumer products, or from *in vivo* formation in the human stomach, is probably ubiquitous. Although other environmental esophageal carcinogens may exist, for example in bracken fern or in opium, they have yet to be identified. At present, the sole contenders for the role of initiators of esophageal cancer in man are the nitrosamines.

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It is only in a few instances that a high rate of esophageal cancer associates with a high exposure to nitrosamines. Usually the levels of exposure, while they could be initiating malignant changes in the genetic material of a few basal cells of the esophagus, are apparently too low to cause symptomatic cancer. However, the initiated cells do progress to form tumors when the action of the nitrosamines is promoted by secondary risk factors. Many of these promoters, including alcohols, deficiency of riboflavin or zinc, and mycotoxins, have been shown to increase the rate of replication in the basal cells of the esophagus. A very plausible working hypothesis is therefore that the cancer is initiated by nitrosamines, and promoted by one or more of the secondary risk factors. The epidemiological and animal studies described in this volume give support to this concept.

The fact that esophageal cancer is one of the most unpleasant forms of cancer, and is one with an exceptionally poor prognosis, make a study of the etiology imperative. In spite of this, the proportion of research effort put into study of the esophagus has been exceptionally low in most developed countries. Knowledge of the basic enzymology and ultrastructure is almost non-existent. The reason is obvious: it is far easier in animal experiments to study an organ such as liver than a small tube such as esophagus. As stated nearly 20 years ago (Wynder *et al.* 1975), 'we need to study the biochemistry of epithelial cells in the upper alimentary and upper respiratory tracts – a far more pertinent target of study than the liver cells. We should not act like the drunk who looks for his lost keys under the lantern simply because that is where the light is and look only at the liver cell because it is relatively an easy system to investigate. We believe that an understanding of the biochemical framework of the squamous cell of the upper alimentary tract of an alcoholic and knowledge of why it is more susceptible to tobacco carcinogens will provide major clues to the biochemical parameters controlling the transformation of a squamous cell into a neoplastic cell.' Sadly the majority are still behaving like drunks, even though modern techniques make study of the esophagus more approachable.

The dramatic epidemiology of esophageal cancer shows that the causes lie in the environment, and suggest obvious measures for prevention. It was stated in 1982 (van Rensburg) that we were 'on the threshold of a period that may be dominated by preventive intervention'. At present, owing to the neglect of basic work, we are still only on the threshold.

The few books and reviews considering the etiology of esophageal cancer are now out of date or limited in their scope to one country. It is now ten years since publication of the excellent reviews of Day *et al.*

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(1982*a*, *b*), and the book edited by Pfeiffer (1982). Several books entitled *Cancer of the Esophagus* have appeared but they have not discussed the general problem of etiology. The excellent book edited by Huang *et al.* (1984) deals mainly with conditions in China, that by DeMeester *et al.* (1985) is devoted almost entirely to diagnosis, pathology and treatment, and that of Matthews *et al.* (1987) to incidence of cancer in the UK. Recently a brief review (Craddock 1992) has been published.

This book has been written in an attempt to draw attention to the fascinating concepts relating to the etiology of esophageal cancer, and to stimulate work which might lead to a reduction in the high incidence of this tragic, preventable disease.

References

Craddock, V.M. (1992) *Eur. J. Cancer Prev.* **1**, 89–103. Etiology of esophageal cancer: some operative factors.

Day, N.E., Munoz, N. and Ghadirian, P. (1982a) In: *Epidemiology of Cancer of the Digestive Tract* (Correa, P. and Haenszel, W. eds.). Dordrecht: Martinus Nijhoff, pp. 21–57. Epidemiology of esophageal cancer: a review.

Day, N.E. and Munoz, N. (1982b) In: *Cancer Epidemiology and Prevention* (Schottenfeld, D. and Fraumeni, J.F. eds.). Philadelphia: Saunders, pp. 596–623. Esophagus.

DeMeester, T.R. and Levin, B. (1985) *Cancer of the Esophagus*. New York: Grune and Stratton.

Huang, G.I. and K'ai, W. (eds.) (1984) *Carcinoma of the Esophagus and Gastric Cardia*. New York: Springer.

Matthews, H.R., Waterhouse, J.H.A., Powell, J., Robinson, J.E. and McConkey, C.C. (1987) *Clinical Cancer Monographs*, vol. I. London: Macmillan. Cancer of the Oesophagus.

Parkin, D.M., Laara, E. and Muir, C.S. (1988) *Int. J. Cancer* **41**, 184–197. Estimates of the world-wide frequency of sixteen major cancers in 1980.

Pfeiffer, C.J. (ed.) (1982) *Cancer of the Esophagus*, vols. I and II. Boca Raton: CRC Press.

van Rensburg, S.J. (1982) *S. Afr. Cancer Bull.* **26**, 153–159. Nutritional factors in human carcinogenesis.

Wynder, E.L., Hoffmann, D., Chan, P and Reddy, B. (1975) In: *Persons at High Risk of Cancer. An approach to Cancer Etiology and Control* (Fraumeni, J.F. ed.). New York: Academic Press, pp. 485–501. Interdisciplinary and experimental approaches: metabolic epidemiology.

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2

Biology of the esophagus

The esophagus is a relatively simple tube which is well adapted to fulfil its function of transporting material from the mouth to the stomach. The elasticity of the mucosa and musculature allows for extension of the lumen during the passage of a bolus of food, and a coordinated nerve plexus and musculature enables peristaltic waves of contraction and relaxation to propel the contents of the lumen to the stomach. On the other hand, the esophagus is one of the first organs to encounter toxic and carcinogenic chemicals in the diet, and the fact that esophageal cancer is one of the cancers with the highest incidence world-wide (Parkin *et al.* 1988) implies that biochemical defence mechanisms are not sufficiently well developed to protect man against this hazard. While the structure and physiology of the esophagus have been studied in some detail, the biochemistry has been almost completely neglected.

Structure of the normal esophagus

The esophagus is comprised of a straight muscular tube running from the pharynx to the stomach. In the neck region it lies dorsal to the larynx and to the anterior end of the trachea, but in the thorax it is slightly to the left of the trachea. After piercing the diaphragm, the esophagus enters the stomach in the middle of the lesser curvature. It therefore lies mainly in the thorax. The length of the esophagus obviously varies very much with the species of animal. In man it is about 25 cm long, in the rat 5 cm.

While an interesting variety of modifications of the esophagus occur in lower animals, in mammals the histological structure follows a common pattern (Figs. 2.1–2.4). The lumen is lined by stratified squamous epithelium, which rests on a corium of connective tissue, the basement membrane. In mammals, the stratified squamous epithelium of the external

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body surface is continuous with that of the oral cavity, which in turn is continuous with the esophagus. The epithelia differ in their embryonic development, however, as that of the epidermis and oral cavity are ectodermal in origin, while the esophageal epithelium is derived from endoderm.

During embryonic development, the esophagus and stomach are derived from the foregut. During the fifth week of pregnancy in man, the stomach appears as a dilation in the foregut, and during the seventh week the cervical flexure is reduced, the neck forms, and the back straightens. At the same time, the esophagus lengthens. The esophageal epithelial cells proliferate and undergo developmental changes which are unique to the esophagus and are not shared by other stratified squamous epithelia (Johns 1952). The epithelium is at first simple low columnar, and at the ninth week of pregnancy it becomes ciliated. At the eleventh week ciliated cells begin to be replaced by squamous cells. Ciliated cells disappear last from the upper end of the esophagus, although patches of ciliated cells may remain at birth and for a short time after birth. Superficial glands are present at birth, but deep glands are scanty, most of their development being post-natal. In other mammals, no ciliated cells appear in the esophagus during embryonic development.

A complete basal layer of cuboid replicating cells rests on the basement membrane. After replication, one or both of the daughter cells may be displaced away from the underlying connective tissue and move upwards towards the lumen. The cells differentiate as they move towards the surface, forming first larger spinous cells, then polygonal granular cells, and finally becoming flatter and giving rise to squamous cells which may or may not produce keratin (Fig. 2.3) (Leblond *et al.* 1984). Blood vessels do

Fig. 2.1. Diagrammatic representation of transverse section of rat esophagus.

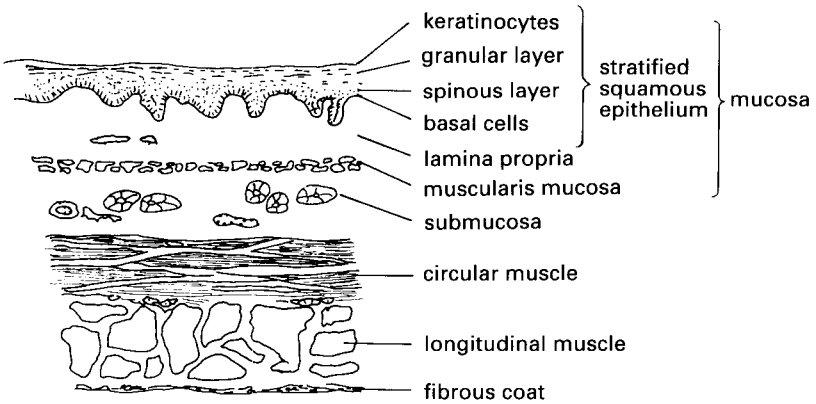

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Fig. 2.2. Transverse section of rat esophagus. C, circular muscle; FC, fibrous coat; L, longitudinal muscle; LP, lamina propria; M, mucosa; MM, muscularis mucosa; SE, squamous epithelium; SM, submucosa. H&E, ×200.

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Fig. 2.3. Transverse section of rat esophageal epithelium. B, basal cells; G, granulocytes; K, keratinocytes; S, spinocytes. H&E, ×1000.

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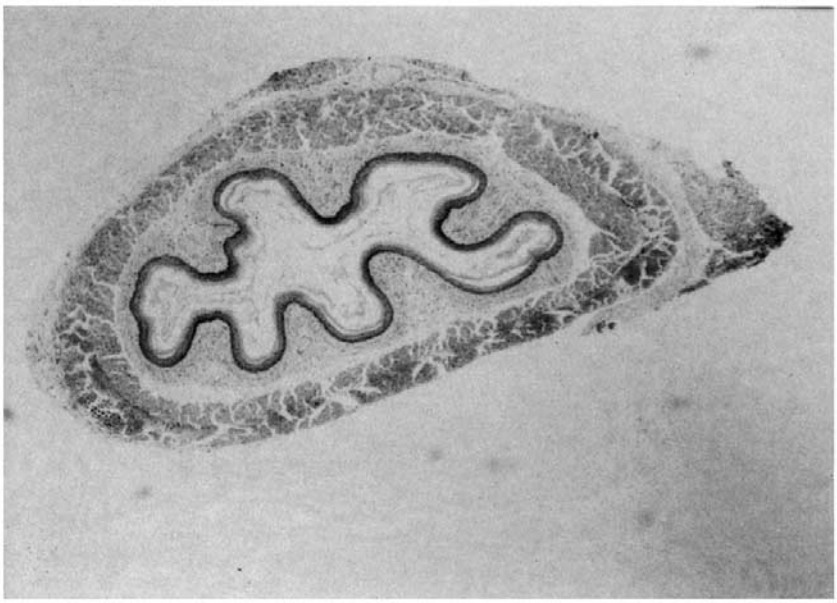
not extend into the epithelium, so that the supply of nutrients decreases as the cells move away from the basement membrane. As a result they become less metabolically active, the flattened cells being relatively inert.

The luminal surface of the esophagus is adapted to protect the epithelium, depending on the type of food normally consumed by the animal. For protection against the coarse vegetable food consumed by rodents, ruminants and the horse, the surface of the epithelium is keratinized. In the superficial cells the nuclei regress, and squames of keratin are continuously shed into the lumen. In the newborn mouse, however, and possibly in other newborn rodents and ruminants, the surface cells are not keratinized but produce mucus, and nucleated cells are shed into the lumen (Parakkal 1967). Surprisingly, in adult rodents there are no glands to provide mucus to lubricate the food bolus.

In man, monkeys, cats and dogs, keratinization is rare, unless it has been caused by trauma, although flattened cells in the superficial layers contain a few keratinohyaline granules. Layers of flattened hexagonal nucleated cells are shed from the surface. Instead of keratinization, protection is afforded by production of mucus, which is secreted through small orifices into the lumen.

In man, the mucus glands are of two types, which secrete different types

Fig. 2.4. Transverse section of rat esophagus to show mucosa thrown into folds which allow expansion during passage of food bolus. H&E, ×12.



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of mucus and differ in their staining properties. The superficial glands occur in the mucosa, and are limited to narrow zones near the two ends of the esophagus. As they resemble the glands in the cardiac end of the stomach, they are sometimes referred to as cardiac glands. The deep glands occur in the submucosa, and are scattered throughout the length of the esophagus, usually predominating in the upper region. The number of glands varies greatly in different individuals.

In the pig, an increasingly popular experimental animal for work on the alimentary canal, the situation is intermediate between that of man and rodents, as keratinization is partial but not complete, and mucus glands are present but are limited to the upper part of the esophagus. The cat is also unusual in being protected neither by mucus glands nor by keratin. These species differences are important to bear in mind when relating the results of experimental work on animals to the situation in man.

In the rat and the mouse, the stratified squamous epithelium of the esophagus continues into the stomach and forms the forestomach. As food passes rapidly down the esophagus and remains in the stomach often for some hours, it has been suggested (Grice 1988) that the forestomach could act as an experimental model for the effect of carcinogens on the esophagus in man. However, although the histological structure of the rodent esophagus and forestomach are very similar, the two organs are susceptible to different carcinogens. In contrast to the situation in rodents, in man there is an abrupt transition from stratified squamous epithelium to simple columnar epithelium at the junction of the esophagus with the cardia of the stomach. Here the white mucus membrane of the esophagus changes abruptly to the pink of the gastric mucosa.

Below the stratified squamous epithelium is a layer of loose connective tissue, the lamina propria. Among the thin collagenous fibres and the network of fine elastic fibres are numerous scattered cells. These cells are mainly lymphocytes, which in man occasionally form small lymphatic nodules, located especially around the ducts of the mucus glands. In addition, plasma cells, macrophages, and eosinophils are present, the numbers rapidly increasing after injury. As mentioned above, in man and certain other species the lamina propria also contains mucus glands.

The lamina propria is separated from the submucosa by the muscularis mucosa. This layer is composed of circular and longitudinal smooth muscle fibres. It is more apparent in lower regions of the alimentary canal, and in view of the fact that it is said to be absent in the mouse (Hummel *et al.* 1966) it may not have an important role in the esophagus.

The submucosa is composed of dense connective tissue, and is fibrous rather than cellular in nature. Broad coarse elastic and collagen fibres are

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present. The major part of the blood supply to the esophagus reaches the organ at the submucosa, where the arteries branch and pass up to the mucosa and down into the muscle layers. The pink muscle layers are well vascularized to provide oxygen for the repeated contractions involved in peristalsis, while the pale mucosa has a poor blood supply. As a result the mucosa is very sensitive to the nature of material passing down the lumen, and to the gastric juice which is regurgitated from the stomach during reflux. The veins from the mucosa and the muscle anastomose in the submucosa, and leave the esophagus beside the arteries. Lymphatics arise as blind tubes in the mucosa, and anastomose to form larger vessels in the submucosa.

The muscle layers occur below the submucosa. Apparently there is a difference of opinion concerning the nature of the muscle fibres in man and animals. In man, the generally accepted view, expressed by Stinson and Reznik (1982), is that the upper third is composed of striated fibres and the lower third of smooth fibres, while the two types are intermingled in the central region of the esophagus. On the other hand, according to Heading (1984), and as he says contrary to popular belief, only the proximate 3–4 cm of the human esophagus contains striated muscle. For ruminants and rodents, according to Stinson and Reznik (1982), the entire length of the muscle layer is composed of striated muscle, while other publications state that the upper, central, and lower thirds of the esophagus have striated, mixed, and smooth muscle fibres respectively. It is unfortunate that this state of confusion has not been resolved.

The arrangement of the two layers of fibres is similar to that which occurs throughout the alimentary canal. The fibres run in a circular direction round the esophagus in the inner layer, and are longitudinally arranged in the outer layer. However, in neither layer is the organization regular and uniform, and obliquely running fibres are present in both layers.

Contraction of the longitudinal muscle shortens the esophagus, while contraction of circular muscle constricts the lumen, and throws the mucosa into longitudinal folds. As the circular muscle has tonus, the normal state of the mucosa is folded (Fig. 2.4). It is the circular muscle which is thickened at the pharyngeal-esophageal and esophageal-gastric sphincters, and tonus results in the sphincters being closed, except when relaxation occurs as a consequence of swallowing. The ganglionated nerve plexuses which control peristalsis are situated in the muscle layers, the myenteric plexus of Auerbach between the inner and outer muscle layers, and the submucosa plexus of Meissner between the submucosa and the circular muscle.

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