CROFTON AND DOUGLAS’S RESPIRATORY DISEASES

EDITED BY

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The late A. GORDON LEITCH BSc, MB, PhD, FRCPE, FCCP

FIFTH EDITION

IN TWO VOLUMES
VOLUME 1
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A decade has passed since we wrote the previous edition of Crofton and Douglas, in conjunction with our late colleague Gordon Leitch. Gordon’s untimely death, giving his life while saving those of others, was a very sad blow not only to his family but also to his many friends and colleagues in Scotland and over the world. His work in the control and management of tuberculosis continued in the footsteps of Sir Robert Philip and Sir John Crofton, and he would undoubtedly have made a most important contribution to the international battle against the disease had he survived. He was also a splendid all-round physician; something of the flavour of this comes across in the chapters he contributed to this book and which he delivered to us just the day before he left on his tragic holiday.

The first edition of this book was published in 1969, at the end of an era in which medical research had made the most notable contributions to the direct care of patients and to the prevention of disease, marked by the discovery of antibiotics and antituberculous chemotherapy, the demonstration of the harmful effects of smoking, and the elucidation of the structure of DNA. The original volume was a relatively slim one, written by our distinguished predecessors, John Crofton and Andrew Douglas, who had themselves played a major role in the battle against tuberculosis. At that time, respiratory medicine was looking towards an uncertain future, as tuberculosis declined and other respiratory diseases remained firmly in the realm of the generalist. Crofton and Douglas’s Respiratory Diseases was perhaps the major factor in helping chest physicians of that era find their new role, allowing us to assert the importance of respiratory disease as a cause of morbidity and mortality in both the developed and poor worlds.

The intervening three decades have seen great changes in the practice and basic science of respiratory medicine, which is now recognized as a main-line acute specialty responsible for the care of a high proportion of the sick in all countries. That our patients are often from the least privileged sections of society has meant that funds for research and clinical care have not always been so easy to obtain as in more glamorous disciplines, but we can look back with some satisfaction to the control of tuberculosis in Britain and the improved outlook for young victims of cystic fibrosis. We have, however, made little impact on the prognosis of lung cancer, have not had as much success as we would have liked in the battle against the amoral tobacco industry, and have watched in dismay as poor medical practice in other countries has encouraged the development of multi-drug resistant tuberculosis. And, in spite of all the research in the subject, we have seen asthma become progressively more prevalent in children. In our day-to-day care of sick patients, we must not take our eyes off the public health aspects of our specialty.

The previous edition of this book was well-received, and its translation into Greek and Italian, together with its production in a low-cost Asian edition, served as a reminder to us of the need to write for a world-wide readership. In this edition, we have reflected the increase in understanding of disease processes that has accrued from basic research, but we have also endeavoured to maintain the tradition of writing for the practising physician, who sees a multitude of patients with diseases common and rare, and who needs guidance on diagnosis and management. We are grateful to a number of friends and colleagues for agreeing to contribute to this edition and believe that their chapters, emphasizing the common and important, will contribute greatly to the value of the book.

One of the benefits of writing a book such as this is the amount one learns or re-learns by reading the references necessary to check up on one’s statements. We have maintained a substantial bibliography, and this includes a number of older references that give graphic original accounts of diseases. It is not uncommon for old lessons to be forgotten and omitted from modern databases; while no textbook can hope to be as up-to-date as these databases, we hope we will help readers to avoid missing important earlier work while still keeping abreast of recent advances. We see this as a book to be used on the ward and in the office, where clinical problems arise and questions are asked and need clear answers.

Anthony Seaton
Douglas Seaton
The observant reader will have noticed the similar names of the two editors. We should like to acknowledge certain aspects of our genetic and environmental heritage. Our late father, Dr Ronald Seaton FRCP, was a pioneer in antimalarial chemotherapy. He inspired us to become doctors and passed on to us a broad, lively and sometimes slightly cynical interest in medicine. From our mother, Julia, a nurse who worked with Lord Moynihan in Leeds and is still busy looking after others as she approaches her tenth decade, we have inherited an aversion to a moment’s idleness. We have been fortunate in our teachers, notably the late Harold Edwards who introduced us to biology and evolutionary theory at school, Dr Colin Ogilvie of Liverpool who first interested us in respiratory medicine, and Professor Keith Morgan who introduced us to the scientific basis of clinical and preventive medicine in the wilds of West Virginia, USA. Many other teachers and colleagues have of course influenced us and continue to do so, not least our juniors who impose a constant challenge to keep up-to-date.

With respect to the production of this book, we acknowledge with gratitude the tolerance of Blackwell’s over our problems with deadlines and, especially, the courtesy and efficiency of Anna Woodford and the production staff. Our thanks also to the copy editor Jo Phillips for his attention to detail and his patience. We should also like to acknowledge the help of Dr Keith Kerr in providing pathological photomicrographs, Dr Lesley Gomersall for help in providing radiographs, and the Medical Illustration Department of Aberdeen University Medical School.

Most importantly, we record our gratitude to our wives, Jill and Anja, for putting up with our prolonged absence at our computers and for nevertheless helping and supporting us throughout this protracted endeavour. We promise to spend more time with them in future.
The respiratory system brings air into close relationship with the mixed venous blood, allowing tissue respiration by uptake of oxygen into the circulation and elimination of carbon dioxide. In addition to this primary function, the lungs have other functions, for example water balance, the maintenance of pH, elimination of inhaled particles and organisms, filtration of particulate matter from the circulation, and metabolism of certain drugs and enzymes. They also serve as a vehicle for the administration of anaesthetic and other drugs. The intimate contact between inspired air (with the multiplicity of organisms, particles and gases that it contains) and the internal epithelium of the lungs (with a surface area some three times that of the body) leads not only to efficient gas exchange but also to repeated opportunities for damage to the lungs and absorption of harmful substances into the body. In order to understand both the normal function of the lungs and the pathology of the diseases with which this book is mainly concerned, it is useful to know something of the development and structure of the organ. In particular, it is now becoming clear that subtle influences on the development of the lung \textit{in utero} and in the early months of extrauterine life may have important effects on lung health in later life, and that the seeds of later chronic airflow obstruction may be sown during the period of intrauterine lung development.

**Development of the lungs**

**Development of the airways and vessels**

The lung appears first as an epithelial bud at the caudal end of the laryngotracheal groove on the 26th day after ovulation \[1,2\]. It thus shares its origin with the foregut, reflecting the evolution in our invertebrate ancestors of a respiratory apparatus from the food-sieving mechanism. This bud, derived from endoderm, will form the epithelium of the airways and of the acini. As it elongates, it becomes invested in mesenchyme derived from mesoderm, and this mesenchymal layer exerts control over its pattern of branching \[3\]. The mesenchyme itself develops into the connective tissue, cartilage, smooth muscle and vessels of the lung. In the first few weeks of development, nerve fibres arising from the ectoderm migrate into the mesenchyme to give the lung its motor and sensory connections \[4\].

The developing lung bud divides into two halves and elongates, growing caudally on either side of the oesophagus. By about 33 days the trachea has become separated from the foregut, and pouches representing the five lobes are clearly apparent. Subsequent dichotomous division leads to the development of the full adult complement of segments by 41 days and to completion of the bronchial tree as far as the terminal bronchioles by 16 weeks \[5\]. While the embryonic lung is developing, changes are also occurring in the circulatory system \[6\]. The primitive branchial arches come and go, leaving the third to form the carotids, the fourth the aorta and the sixth the pulmonary trunk (Fig. 1.1). This appears at about 32 days, becoming separated from the primitive truncus arteriosus by the development of a spiral septum, and joins the vascular plexus that has already formed in the lung bud. By 37 days, the single ventricle of the heart has divided into two chambers, the blood supply to the lungs coming from the right side. At this stage the right sixth arch artery has disappeared and the lung’s main blood supply, the pulmonary artery, comes solely from the left arch. Its branches divide approximately in correspondence with those of the bronchial tree, but so-called supernumerary arteries occur with increasing frequency towards the periphery and supply structures adjacent to the main bronchi. Ultimately they will supply alveoli of neighbouring acini when these have developed. Before the formation of this pulmonary arterial supply, the lung receives its blood from pairs of segmental arteries arising from the aorta above the coeliac axis in the region of the fetal neck. These arteries migrate caudally and eventually disappear, being replaced by new bronchial arteries that arise from the aorta between about 9 and 12 weeks. The persistence of the original primitive bronchial arteries is the explanation for the occasional supply of sequestrated...
lung segments by a transdiaphragmatic artery from the aorta above the coeliac axis, a potential hazard well known to thoracic surgeons [7] (Fig. 1.2).

The venous drainage of the developing lungs is initially into the systemic cardinal and postcardinal veins and the visceral veins of the abdomen. These develop into the two venae cavae, the innominate vein and their tributaries. By about 10 weeks a diverticulum arises from the left atrium that connects with those veins draining the lungs, so that the four pulmonary veins finally enter the left atrium. Abnormalities in this development result in anomalous pulmonary veins leading into the vena cava or right atrium or a separate chamber connected to the left atrium, cor triatriatum [8]. Drainage of the right lung by an anomalous vein into the inferior vena cava gives rise to the scimitar sign on the chest radiograph (Fig. 1.3). Thus, by about 16 weeks of intrauterine life, the preacinar structures of bronchi, pulmonary arteries and veins, and bronchial arteries are all present in the numbers and anatomical distribution that they will maintain throughout life. However, important changes are still to occur in these structures at the microscopic level, while they have of course to grow and the acinar structures to develop.

**Cellular development of the lung**

Until about 16 weeks, the developing lung has a pseudoglandular appearance, i.e. narrow tubes surrounded by a cuboidal or columnar epithelium on a basal lamina and in a mesenchymal stroma [1,9,10]. By 16 weeks, both goblet cells and mucous glands have developed and ciliated cells are present throughout the bronchial epithelium. From 16 until about 26 weeks the lung’s appearance is described as canalicular. The epithelium thins out, the cells becoming flatter and the future air spaces larger. The mesenchyme becomes very vascular, and as the more peripheral airways develop their epithelium becomes very thin, allowing close approximation of blood to the air space. This is a period of rapid growth, during which the lung’s DNA doubles [11].

These terminal saccules become well defined towards 26 weeks, when the appearance of the lung is described as saccular. By this time type I and type II pneumocytes can be identified in the saccular epithelium and osmiophilic bodies appear in the type II cells, indicating that the lung has developed the ability to secrete surfactant. This production of surfactant may be promoted by the administration of glucocorticosteroids to the mother in some species [12], a fact that is relevant in improving the survival chances of premature infants. Meanwhile, cartilage, which appears in the trachea at 4 weeks and gradually spreads down the airways to reach segmental bronchi at 12 weeks, has by 26 weeks developed far down the bronchial tree, though further extension occurs until the early weeks of postnatal life. Similarly, smooth muscle, which first appears in the lobar bronchi and above at about 6 weeks, has also spread down to the terminal bronchioles. In the pulmonary arteries smooth muscle appears at about 12 weeks and has reached vessels at the level of the terminal bronchiole by 26 weeks; this vascular smooth muscle will grow further down the arterial tree after birth, reaching alveolar walls in adult life. Thus the lung at about 26 weeks has reached a stage of maturity at which it is capable of supporting life.

The rest of the time spent in utero, from 26 weeks to term, is occupied by the development and subdivision of the respiratory bronchioles and their saccules, with a variable amount of alveolar development, and by the growth of the airways. At one time it was thought that there were very few alveoli present at birth, but more recent studies have
shown that some alveoli may be present as early as 30 weeks and that as much as 50% of the final adult number may be evident at the time of birth, though this proportion is very variable [13,14].

**Postnatal development**

At the time of birth there is an adult complement of about 24 million terminal bronchioles [15–17]. From the time of birth there is an initial rapid increase in the numbers and then in size and complexity of alveoli, which start appearing *in utero*, first on the peripheral saccules and then up towards the proximal respiratory bronchioles. Some may even develop on the terminal bronchiole. Some 127 million alveoli are present at about 1 year and most by the age of 2; the final adult complement of about 280 million may have developed by the age of 8, although some authorities suggest that alveolar multiplication continues at a slower rate until somatic growth ceases, the numbers in adults being estimated to vary between 200 and 600 million. Growth of the airways and modelling of the lung to match the shape of the thorax and its contents continues until the body stops growing. Any abnormality of shape of the thoracic cavity will affect this; for example, a congenital diaphragmatic hernia, when the normal separation of thoracic and abdominal cavities does not occur at 7 weeks, causes a small lung in which the numbers of both airways and alveoli are reduced [18], while kyphoscoliosis developing in early childhood causes a small lung with reduced alveolar numbers [19]. Other important influences on airway or alveolar development are fetal nutrition, which if impaired in mid-gestation may result in smaller or even fewer airways, and oligohydramnios, which may constrict lung growth and lead to smaller airways [20,21]. These influences are currently a matter of considerable research interest to those who wish to understand why one person

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Fig. 1.2 Aortogram showing aberrant arterial supply of sequestrated lung segment from aorta.