INTRATHORACIC DUPLICATIONS OF THE FOREGUT

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PART II

CLINICAL IMPLICATIONS

Diagnosis

Awareness of duplication is the prerequisite to correct diagnosis. Chest radiographs of all patients presenting with unexplained mediastinal masses should be carefully examined for spinal deformities. All infants and children with swellings of the mediastinum of unknown origin should have antero-posterior and lateral films of the vertebral column, including the cervical spine. The finding of spina bifida, fused cervico-dorsal vertebrae and other associated congenital spinal deformities should immediately suggest the possibility of foregut or intestinal duplications. When a vertebral lesion co-exists with a mediastinal duplication, especially of the elongated type, the co-existence of an intestinal duplication becomes probable. When the subject in addition loses blood in the stool and complains of vague, periodic colicky pains in the abdomen, this association becomes a certainty. Endoscopy and bronchograms are seldom helpful but a barium swallow is useful and should always be done.

Complications

Symptoms may be absent, slight, or so severe as to demand emergency measures. Duplications of bronchial origin seldom give rise to serious complications in the adult but may cause compression and thus give rise to respiratory distress, dysphagia or bone erosion, which might be particularly dangerous in infants. On the other hand duplications of alimentary origin are potentially extremely dangerous, especially in infants and children, where mild warning symptoms may either be unnoticed or wrongly interpreted. Complications are more the rule than the exception,[36] and fatal termination is not uncommon[72,69] (case 5 in this series). Active peptic ulceration is common; it may lead to haemorrhage and perforation with all its concomitant sequelae. The inflammatory reaction around the ulceration is most intense and may result in dense adhesions to neighbouring structures. Fistulae may form into the bronchus,[31] the lung,[50] the oesophagus,[37] and the pericardium (case 5). The cysts may become infected, or may cause obstruction, either by predisposing to volvulus[42] or by encroaching on the lumen of the gut.[67] Dohn *et al.*[20] found that 60% of the subjects with enterogenous cysts which they reviewed in 1952 had intestinal obstruction, and 25% of the total were fatal.

Treatment

Because of the danger of complications and the uncertainty in the diagnosis there is no place for conservative treatment in suspected duplications of the foregut. Anaesthesia and thoracic surgery are now sufficiently advanced to urge surgical extirpation without hesitation in any age-group. The diaphragm should be incised and the abdomen explored if there is any indication of a prolongation downwards. If the cyst wall forms part of the membranous trachea, the mucosa only should be removed here and the muscle left behind.

THEORIES ON THE ORIGIN OF DUPLICATIONS

The multiple theories that have been advanced to explain duplications on an embryological basis are sufficient evidence of their complexity. From the above case histories and comments it is clear that the different types of foregut duplications sometimes merge imperceptibly into one another. Furthermore the relationship between mediastinal and abdominal duplications and other anomalies is so constant and similar that a theory cannot be accepted if it fails to take into account all the variables. Finally the common characteristics of certain congenital syndromes and abnormalities suggest a common denominator. Theories should be critically examined in this light.

1. *Vitelline Theory*

Since Meckel's original description of the intestinal diverticulum which still carries his name, this vitelline vestige has been included in the list of possible causes of intestinal duplications. It is hardly necessary to point out that in Meckel's diverticulum there is a 5 to 1 sexual preponderance of males;[15] that associated anomalies are not commoner than in the average population, and that it is difficult to understand how duplications in the oesophagus and rectum can arise from this source. Further, Edwards[21] reported a typical Meckel's diverticulum in a patient with a duplication and quite rightly concluded that two diverticula of Meckel

do not occur in the same bowel. This view is now only of historic interest. Black *et al.*[5] regarded intrathoracic duplications as vestigial intrathoracic remains of vitelline veins. However, at the time of obliteration of the vitelline duct, the vessels of the dorsal mesentery are well developed, and these cysts should be vascularized by mesenteric vessels, which is difficult to imagine when they occur in the rectum or at the base of the tongue.

2. *Theory of Diverticulation*

Lewis and Thyng[49] found that knob-like diverticula are commonly present in the foetal alimentary tract of pigs, rabbits and man. These normally regress, but the authors suggested that persistance or sequestration might give rise to duplication. The fact that duplications are most commonly found in the terminal ileum where foetal diverticula preponderate has been used further to strengthen this argument.

Confusion is caused by the inappropriate use of the loose term 'diverticulum'. Meckel's diverticulum for instance is embryologically and pathologically not cognate with the embryonal out-pocketing seen by Lewis and Thyng.[49] Yet abnormal differentiation of epithelium, such a characteristic feature in duplications, is not uncommon in a Meckel. Congenital diverticula of the alimentary tract are usually more or less of the same size, are known to preponderate in certain areas of the gut, are often multiple, and share the same epithelial and muscular layers as the parent organ at that level. Congenital diverticula should also be differentiated from the acquired type of pulsion diverticulum (commonly at the crico-pharyngeus and lower end of the oesophagus), the traction diverticulum (at the hilum of the lung), and those that develop along the path of larger blood vessels, especially in the colon and small intestine. Even some of these so-called acquired diverticula may be congenital, characterized by the same features as duplications. For instance, Baar *et al.*[3] described a case of epiphrenal oesophageal diverticulum containing the normal layers of the oesophagus but connected to the lung by a band of functioning pancreatic tissue, which proved its congenital origin. There is no evidence that diverticulation occurs in the developing oesophagus, and there is certainly no association with spinal deformities, as there is in duplication of oesophageal origin. Whereas it is possible that congenital diverticula of the gut develop as a persistance of the above-mentioned epithelial buds,[49] it is hardly conceivable that these simple, uniform aberrations would grow and develop into complex duplications anywhere from the pharynx to the anus. All the facts suggest two entirely different entities, if not in origin then at least as end results.

3. *Theory of Vacuolization*

Shallow[73] and Keith[40] felt that duplication results from failure of, or abnormal coalescence of vacuoles, and Bremer[12] still blames abnormal vacuolization for all duplications. He supports Lewis and Thyng's theory that diverticula develop as minute hollow buds from the epithelial lining of the gut, which grow into the subepithelial connective tissue in embryos of 20 - 30 mm. Most of these disappear, but some persist and may with development push through the outer layers as a pedicled diverticulum or close off as a free cyst. Duplications, he holds, are formed at the time of epithelial proliferation and rapid elongation of the gut, and are due to persisting vacuoles which fail to communicate with the parent lumen.

Contrary to a misconception which still lingers, I find that the lumen of the oesophagus is never completely occluded, but its size varies considerably at different levels and during different stages of development. Before the embryo reaches 10 mm. the lumen is already established; vacuoles only appear by about 12 mm.[7,8] The caudal end of the oesophagus elongates rapidly and is by far the narrowest part, a feature which probably led to the belief[44] that the lumen becomes occluded by epithelial proliferation and later re-established by vacuolization, a process which is well known to occur in the oesophagus of certain lower vertebrates.[68] After a study of serial sections through the oesophagus in embryos varying from 12 to 14 mm., I was never satisfied that the confluence of vacuoles, which in some areas was completely absent, contributed substantially to the lumen. At 29 mm., when the vacuoles were most conspicuous, the lumen was already relatively large, and although vacuolization continues till about 75 mm., in not one instance was a single vacuole seen outside the developing muscularis mucosae. Even Bremer could not explain complete duplication of the stomach on the basis of abnormal confluence of vacuoles, and postulated that this type of duplication was due to fusion of opposing walls. It is equally difficult to believe that vacuoles can give rise to a double colon with two perfectly formed separate appendices, or a second oesophagus which stretches from the root of the neck to the 12th thoracic vertebra through an accessory diaphragmatic hiatus.[45] The main reason why vacuoles cannot possibly be a causative factor for elongated duplications is that they appear too late in the embryo to derange certain fundamental embryological developments. Thus, spinal abnormalities cannot be explained on such a hypothesis.

4. *Theory of Imperfect Separation of the Tracheopulmonary Bud from the Oesophagus*

The theory of Olenik *et al.*[59] that all cysts are derived from the foregut at or near the origin of the lung buds might explain some mediastinal duplications but fails to account for those which occur elsewhere. The same objection may be raised against Bergmann *et al.*,[4] who thought it apparent that tracheobronchial rests in the oesophagus as well as tracheo-oesophageal fistula are the results of failure of the normal embryonal process of separation of the respiratory tract from the primitive oesophagus. The predominance of simple bronchogenic cysts in the superior mediastinum and their common intimate connection with the tracheobronchial system suggests that many of them might arise at the site of separation. That this may not necessarily be a simple local process is shown by the co-existence of vertebral anomalies in cases with bronchogenic cysts.[77,52] In the present series some of the most typical bronchogenic cysts had no evidence of cartilage in their walls, and the case of bronchogenic cyst with an associated spinal deformity was very similar to the cases quoted by Tucker[77] and Maier.[52] The association of bronchogenic cysts with other anomalies such as cryptorchidism,[39] patent foramen ovale and ductus arteriosus,[38] ductus arteriosus in twins,[16] and congenital cataracts,[19] further suggests that a more generalized embryological disturbance exists. A mere failure of normal separation of the respiratory and alimentary tracts would similarly not explain the common co-existence of tracheo-oesophageal fistula with congenital heart disease, malformation of anus and rectum, malrotation of the gut, abnormalities of the kidney, and atresia of the small intestine. As in duplications, vertebral anomalies, pulmonary aplasia and concomitant intestinal duplications may occur in tracheo-oesophageal fistula. This intrinsic tendency to widespread malformation was admirably illustrated by a case of tracheo-oesophageal fistula in which there were also an imperforate anus and an accessory thumb on the right hand.

5. *Sequestration of Embryonic Multipotential Cells of the Primitive Alimentary Anlage*

A full discussion of the many fascinating facets of sequestration unfortunately falls outside the scope of this paper. I shall only briefly point out the relationship between 'extralobar sequestration' of the lung, of which there are 2 examples in this series, and duplication of the foregut.

The respiratory system arises from a median longitudinal groove in the ventral wall of the pharynx when the embryo is about 3 mm. long. This ventral outgrowth is soon pinched off from the foregut by lateral constrictions, which start caudally and proceed headwards. My own observations support Boyden's view[11] that the primordial trachea then grows caudally, becomes evaginated, and divides into 2 buds which rapidly extend into the surrounding mesenchyme with further branching to form the lobar and segmental bronchi. A disturbance of normal separation may therefore be responsible for a variety of the well-known tracheo-oesophageal defects, or separation may be apparently normal but duplications may form either from the oesophagus proper or the primitive tracheobronchial system. Disorganized growth may also occur later and therefore be evident in a more peripheral part of the bronchial tree. The most minor disturbance occurs when additional buds develop in an otherwise normally developed bronchial system (supernumerary segment) or when the segmental buds are normal numerically but in the wrong position (misplaced segments). These may persist, as is commonly seen in the right upper lobe, and develop as normal fully-functioning units in abnormal positions, served by a patent bronchus and supplied by a branch of the pulmonary artery. On the other hand, these components may degenerate and finally disappear. Small buds of the dissociated tissue may persist and give rise to unilocular or multilocular cysts, which may or may not retain

their connections with the bronchi and may even be wrongly reported as teratomas.[39,38] If abnormal growth occurs even more distally, solitary intrapulmonary cysts may arise or cystic masses of disorganized lung tissue may be formed, with or without systemic pulmonary arteries, known as intralobar sequestrations. These may start to develop *in utero* but, if so, then it is surprising that not a single case was found under 1 year old in over 16,000 necropsies done at different centres.[63,9] However, it does not mean that the condition cannot occur, and one reason why it could be missed easily at necropsy is that the pathological anatomy might be so nearly normal that it escapes notice. As budding might continue for a further 7 generations after birth (18 before birth[34]) the possibility exists that this abnormality might arise or be accentuated in postnatal life. Abbey Smith[74] postulates that when such a segment is supplied by a systemic pulmonary artery and subjected to the high systemic blood pressure cystic changes and fibrous degeneration take place. He could not explain one of his own cases with a 'whole lobe type of lesion' on this theory and, although his theory is attractive and simple, it does not explain why mature individuals with single stout systemic pulmonary arteries[64,65,54] or multiple systemic arteries (5 - 6)[23] do not develop cysts in the segments supplied by those vessels. Finally, Boyden[10] has shown cysts without evidence of systemic vessels and a systemic pulmonary artery without any evidence of intralobar sequestration in 2 embryos of 31 and 41 mm. respectively.

Lung tissue may not only be developed from the conventional source, but also from any other part of the primitive foregut. Again the primary disturbance of growth may be minimal so that solitary cysts may develop within the wall of the oesophagus or outside this organ and contain all the characteristics of a foregut duplication of bronchial origin. If the disturbance in growth is more pronounced, accessory lung tissue may form, known as extralobar sequestration, which may or may not be associated with an ordinary duplication of oesophageal origin. Two cases in the present series are examples of this type. When the connection of the sequestration to the foregut persists it forms irrefutable proof of the origin of the anomaly. Connections to the stomach[71] and the oesophagus at bifurcation level[28] have been described. The extralobar sequestrations are usually supplied by one or more systemic arteries arising directly from the aorta, intercostals or phrenic arteries. These may even reach the size of the aorta.[53] In another case (adult female) that was shown to me, the systemic artery arising from the phrenic was the size of a pencil and supplied a right posterior lower-lobe sequestration. After operation the systemic hypertention dropped to a steady 140 mm. Hg systolic. Weisel *et al.*[81] considered sequestration as bronchogenic cysts with associated anomalous vascular supplies. Cole *et al.*[17] regarded bronchogenic cysts, anomalous systemic vessels, extralobar sequestrations, and diaphragmatic defects, as related conditions with a common developmental error. Caffey[12] included diaphragmatic defects, cardiac and renal malformations, skeletal abnormalities, and absence of the vagus nerve as commonly associated with aplasia of the lung, and further considered the high frequency of association of pulmonary aplasia with hemivertebra to justify the combination as a syndrome. The high preponderance of left-sided lesions (90%[78]) are explained by Bolck[6] on the basis of late closure of the left leaf of the diaphragm, which would also account for the high incidence of diaphragmatic defects.

The theory[64] that both intralobar and extralobar sequestrations are due to traction on one or more buds of the developing bronchial tree by abberrant arteries, while the lung is undergoing developmental shifts, cannot be accepted embryologically. Even in the early stages the bulbous tips are well developed and contain a thick pseudocolumnar epithelium with several rows of cells, while the vascular network is still either non-existent or essentially capillary (Boyden's 'no man's land'[10]) and cannot possibly 'capture' such a stout bronchial bud. There is also no evidence to support the idea that the pulmonary and systemic arteries are competing to capture the lung buds. It seems much more likely that aberrant vessels are persistent branches of the vascular plexus which surrounds the visceral tubes very early in development. When such a channel exists it merely takes over the bud (later to become duplication of bronchial origin or sequestration) in its vicinity and may eventually be moved apart as growth takes place. The differences between intralobar and extralobar sequestrations have been admirably covered by Abbey Smith,[74] and need no further elaboration. The intimate co-existence of an elongated duplication and an extralobar sequestration with systemic arteries (case 5) is beyond doubt.

6. *The Notochordal Theory*

Feller *et al.*[24] (1929) collected 28 cases of malformations which involved both the central nervous system and the alimentary canal; every case also had anterior spina bifida. Puussepp[66] was the first to describe a foregut duplication with the characteristics of small intestine within the vertebral canal; it was lying within the dura dorsal to the cervical spinal cord (C3) in a man of 27 years. Guillery's case[32] is referred to above. Knight *et al.*[43] reported a large duplication characteristic of stomach which was lying within the cord in the cervicodorsal area of a child of 15 months. Recently Harriman[35] reported another 'enterogenous cyst' within the spinal cord at vertebra D3; there were gross vertebral anomalies from C7 to D7. Unlike teratomas, which contain only ectodermal and mesodermal elements, this cyst contained mesodermal and endodermal elements, which were surprisingly well differentiated and orderly. This suggested that the ectopic cyst was extruded into the spinal canal through the anterior spina bifida and might or might not be related to a corresponding tumour in the mediastinum, of which no evidence could be found.

The significance of vertebral anomalies was first noticed by Stoeckel.[75] Veeneklaas[79] suggested that imperfect separation of the notochord from the endoderm may lead to withdrawal of a pouch from the primitive alimentary tube into the mesodermal anlage of the vertebral column, which may then develop into a duplication with or without communication with the digestive tract, while the attachment of the pouch to the notochord may interfere with the normal development of the spine. Fallon *et al.*[29] gives a good account of the notochordal theory and feels that all duplications above and below the diaphragm as well as the various forms of vertebral dysplasia are the result of upset of the stage of excalation of the notochord.

From what has been said before it should be clear that spinal abnormalities usually do not occur in duplications of the lower intestinal tract, although these may be extensive, and further that vertebral anomalies occur typically with certain types of malformation without any apparent involvement of the alimentary tract. I therefore suggest that the primary defect does not lie in the notochord, but that the skeletal and nervous dysplasias are part of the greater or lesser disturbance in development which might affect general systems of the embryo at various levels in many different ways.

7. *Theory of Twinning*

This theory has been rejected in the past but recent work[18] has shown that twin formation may well occur, a theory which would appeal particularly in some of the elongated duplications of the large bowel. Morton[56] published a case of duplication of the pituitary and stomatodaeal structures in a 38-week male infant. In order to explain such a duplication or 'twinning' it is necessary to envisage a stage in the early development during which a small deviation from normal will initiate a chain of events that will bring about the ultimate abnormality in all its variations.

8. *The Imbalance of Organizational Substances in Embryonic Life*

Needham[57] favours 'morphogenetic hormones or stimulating substances' as being important factors in 'many inheritable aberrations or modifications of development.' Baar *et al.*,[3] in their series, explained all duplications and deviations of the foregut 'on the basis of an interference with organizer centres leading to a failure of resorption of accessory buds of the primitive foregut and the displacement of the growing buds within intersections of morphogenetic gradients resulting in a preponderance of self-differentiation over dependent differentiation. . . .'

The hormonal theory has the beauty of simplicity. In my opinion it is the only logical concept that is compatible with all the facts, and the following hypothesis is put forward on this basis:

Localized derangements in embryonal metabolism and hormonal guidance may result in abnormal development of normal tissues. The severity and the time of the upset decides the position, type and extent of the ultimate abnormality. Minor disturbances may be rectified by the organism without

any subsequent trace, or anomalous developments may be incorporated as normal functional units (supernumerary and misplaced bronchi). Localized cysts may also develop at different levels from the tracheobronchial tree or oesophagus, with the characteristic features of the parent organ but no associated anomaly. Abnormal growth may be early and give rise to extralobar sequestration, or possibly late and lead to intralobar sequestration, with or without concomitant congenital vascular anomalies. As a result of one anomaly other disturbances in growth may follow which are not primarily hormonal but mechanical, and such permutations may present bizarre patterns which are difficult to explain. If the disturbance is more severe, round duplications may result which retain their endodermal competence, and because they are out of position and disorganized the histogenic differentiation is less complete and precise. The varied mucosal cell type is merely a reflection of the wide developmental potential of endodermal tissue.

With even more severe or persistent disturbances elongated duplications result which represent the anatomy as well as the physiology of the parent organ to a surprising extent. The upset in local hormonal control spreads to neighbouring or associated organizer centres and high spinal deformities become the rule rather than the exception. Concomitant abdominal duplications and malrotation of the gut now occur, and when the oesophagus is completely duplicated the spinal deformity even involves the sacrum. A less localized disturbance may involve several systems and give rise to typical and well-known syndromes. Minor generalized upsets, or localized upsets occurring at different times, may give rise to apparently unconnected congenital anomalies, while severe hormonal imbalance results in frank monster formation.

Töndury,[76] who reviewed developmental physiology of abnormal growth, is convinced that physical factors act at critical phases to produce abnormalities. Areas of high embryonal differentiation and activity would be most vulnerable. Apart from familial and hereditary predisposition,[41] rubella,[20] uterine bleeding,[56] and tubal pregnancy,[10] foetal abnormalities have been produced experimentally by avitaminosis,[2] hypervitaminosis,[29] irradiation, hormones,[82] and other substances.[26] The local effect of anoxia on foetal bowel has been admirably studied by Dr. C. N. Barnard and Prof. J. H. Louw,[51(a)] and further studies on the general effect of anoxia are in progress at the Department of Surgery, University of Cape Town. The exact mechanism whereby these abnormalities are produced is at present conjectural, and until further data accumulate from experimental embryology the propounding of new theories serves little purpose except to perpetuate the confusion.

SUMMARY AND CONCLUSIONS

Intrathoracic duplications of the foregut were considered in the past as pathological curiosities. In fact they are not uncommon. Awareness of the condition is a prerequisite to diagnosis. The macroscopical and histological features of 26 cases are described with illustrative case reports.

Duplications in the thorax arise either from the tracheobronchial or the alimentary systems, and the differentiation is usually easy but by no means absolute. These structures are potentially dangerous and should always be removed without delay, for the complication rate in those of oesophageal origin, and especially in children, is extremely high. A spinal deformity should always be looked for in the chest films and special views obtained if any doubt exists. Associated intestinal duplications should be kept in mind, especially if vertebral anomalies are present and vague abdominal cramps or blood in the stools are noticed.

Existing theories on the origin of duplications are critically analysed and arguments are substantiated by personal embryological and clinical observations. All evidence suggests that duplications are produced in the same way as other abnormalities; that is to say, by physical and chemical factors that act at critical phases in certain areas of the developing embryo.

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REFERENCES

1. Aken, W. van (1951): Ned. T. Geneesk., **95**, 564.
2. Ancel, P. (1954): Arch. Anat. (Strasbourg), **37**, pt. 2, 1.
3. Baar, H. S. and d'Abreu, A. L. (1950): Brit. J. Surg., **37**, 220.
4. Bergmann, M. and Charnas, R. M. (1958): J. Thorac. Surg., **35**, 97.
5. Black, R. A. and Benjamin, E. L. (1936): Amer. J. Dis. Child., **51**, 1126.
6. Bolck, F. (1950): Virchows Arch. path. Anat., **319**, 20.
7. Botha, G. S. M. (1957): *The Gastro-oesophageal Closing Mechanism.* Thesis for degree of Ch.M., Univ. Birmingham.
8. *Idem* (1959): Anat. Rec., **133**, 219.
9. Boyd, G. (1953): Dis. Chest, **24**, 162.
10. Boyden, E. A. (1958): J. Thorac. Surg., **35**, 604.
11. *Idem* (1955): Amer. J. Surg., **89**, 79.
12. Bremer, J. L. (1957): *Congenital Anomalies of the Viscera.* London: Oxford University Press.
13. Caffey, J. (1945): *Pediatric X-ray Diagnosis.* Chicago: Year Book Publishers, Inc.
14. Cassel, M. A., Cunningham, R. T. and Weisel, W. (1950): J. Thorac. Surg., **19**, 138.
15. Christie, A. (1931): Amer. J. Dis. Child., **42**, 544.
16. Claireaux, A. E. (1951): J. Path. Bact., **63**, 743.
17. Cole, F. H., Alley, F. H. and Jones, R. S. (1951): Surg. Gynec. Obstet., **93**, 589.
18. Corner, G. W. (1955): Amer. J. Obstet. Gynec., **70**, 933.
19. Dabbs, C. H., Berg, R. and Pierce, E. C. (1957): J. Thorac. Surg., **34**, 718.
20. Dohn, K. and Povlsen, O. (1951): Acta chir. scand., **102**, 21.
21. Edwards, H. (1929): Brit. J. Surg., **17**, 7.
22. Ehler, A. E. and Atwell, S. (1948): J. Thorac. Surg., **17**, 809.
23. Fallon, M., Gordon, A. R. G. and Lendrum, A. C. (1954): Brit. J. Surg., **41**, 520.
24. Feller, A. and Sternberg, H. (1929): Arch. Anat., path. **272**, 613.
25. Fisher, H. C. (1950): Arch. Surg. (Chicago), **61**, 957.
26. Fraser, F. C. and Fainstat, T. D. (1951): Amer. J. Dis. Child., **82**, 593.
27. Galloway, W. H., Sutherland, A. M. and Williams, A. W. (1956): Arch. Dis. Childh., **31**, 422.
28. Gans, S. L. and Potts, W. J. (1951): J. Thorac. Surg., **21**, 313.
29. Giroud, A. and Martinet, M. (1955): 6e Congrès Fédératif International d'Anatomie. Paris.
30. Gregg, N. M. (1942): Trans. Ophthal. Soc. Austral., **3**, 35.
31. Gross, R. E. (1953): *The Surgery of Infancy and Childhood.* Philadelphia: W. B. Saunders.
32. Guillery, H. (1937): Zbl. allg. Path. path. Anat., **69**, 49.
33. Halasz, N. A., Halloran, K. H. and Liebow, A. A. (1956): Circulation, **14**, 826.
34. Hamilton, W. J., Boyd, J. D. and Mossman, H. W. (1952): *Human Embryology.* Cambridge: Heffer.
35. Harriman, D. G. F. (1958): J. Path. Bact., **55**, 413.
36. Hollinger, P. H., Johnston, K. C. and Potts, W. J. (1952): Acta oto-laryng. (Stockh.), **100**, 100.
37. Hutchison, J. and Thomson, J. D. (1953): Brit. J. Surg., **41**, 15.
38. Jellen, J. and Fisher, W. E. (1936): Amer. J. Dis. Child., **51**, 1397.
39. Joël, J. (1890): Arch. Anat., path. **122**, 381.
40. Keith, A. (1948): *Human Embryology and Morphology*, 6th ed. London: Edward Arnold.
41. Kemp, T. (1951): *Genetics and Disease.* Copenhagen: E. Munksgaard.
42. Kirkman, N. F. (1957): Brit. J. Surg., **44**, 540.
43. Knight, G., Griffiths, T. and Williams, I. (1955): *Ibid.*, **42**, 635.
44. Kreuter, E. (1905): Dtsch. Z. Chir., **79**, 1.
45. Ladd, W. E. and Scott, H. W. (1944): Surgery, **16**, 815.
46. Ladd, W. E. and Gross, R. E. (1940): Surg. Gynec. Obstet., **70**, 295.
47. Laipply, T. C. (1945): Arch. Path., **39**, 153.
48. Langston, H. T., Tuttle, W. M. and Patton, T. B. (1950): Arch. Surg. (Chicago), **61**, 949.
49. Lewis, F. J. and Thyng, F. W. (1907): Amer. J. Anat., **7**, 505.
50. Linder, H. (1949): Surgery, **25**, 862.
51. Lindquist, N. and Wulff, H. B. (1947): J. Thorac Surg., **16**, 468.
51 (*a*). Louw, J. H. and Barnard, C. N. (1955): Lancet, **2**, 1065.
52. Maier, H. C. (1948): Ann. Surg., **127**, 476.
53. McDowell, C., Robb, D. and Indyk, J. S. (1955): Thorax, **10**, 73.
54. McCotter, R. E. (1910): Anat. Rec., **4**, 291.

55. Mixter, C. G. and Clifford, S. H. (1929): Ann. Surg., **90**, 714.
56. Morton, W. R. M. (1957): Arch. Dis. Childh., **32**, 135.
57. Needham, J. (1939): Ann. Rev. Physiol., **1**, 63.
58. Normark, A. (1938): Acta paediat. (Uppsala), **20**, 475.
59. Olenik, J. L. and Tandatnick, J. W. (1946): Amer. J. Dis. Child., **71**, 466.
60. Olken, H. G. (1944): Amer. J. Path., **20**, 997.
61. Orban, F. and Honoré, D. (1954): Acta paediat. belg., **8**, 150.
62. Oterdoom, H. J. (1951): Ned. T. Geneesk., **95**, 566.
63. Potter, E. L. (1952): *Pathology of the Fetus and the Newborn.* Chicago: Year Book Publishers.
64. Pryce, D. M. (1946): J. Path. Bact., **58**, 457.
65. Pryce, D. M., Sellors, T. H. and Blair, L. G. (1947): Brit. J. Surg., **35**, 18.
66. Puussepp, L. (1934): Rev. neurol., **62**, 879.
67. Ramsay, G. S. (1957): Brit. J. Surg., **44**, 632.
68. Reese, A. M. (1926): Amer. J. Anat., **37**, 195.
69. Roberts, K. D. and Weeks, M. M. (1957): Brit. J. Surg., **44**, 377.
70. Roth, M. (1881): Virchows Arch. path. Anat., **84**, 371.
71. Scheidegger, S. (1936): Frankfurt. Z. Path., **49**, 362.
72. Seydl, G. N. (1938): *Ibid.*, **52**, 346.
73. Shallow, T. A. (1925): Ann. Surg., **81**, 795.
74. Smith, R. A. (1956): Thorax, **11**, 10.
75. Stoeckel, K. N. (1935): Zbl. Gynäk., **59**, 2178.
76. Töndury, G. (1955): Münch. med. Wschr., **97**, 1009.
77. Tucker, G. (1946): Ann. Otol. (St. Louis), **55**, 693.
78. Valle, A. R. and White, M. L. (1947): Dis. Chest, **13**, 63.
79. Veeneklaas, G. M. H. (1952): Amer. J. Dis. Child., **83**, 500.
80. Ware, G. W. and Conrad, H. A. (1953): Amer. J. Surg., **86**, 264.
81. Weisel, W., Docksey, J. W. and Glicklich, M. (1955): Amer. Rev. Tubere., **71**, 573.
82. Woollam, D. H. M. (1958): Ann. Roy. Coll. Surg. Engl., **22**, 401.