Rickham's Neonatal Surgery

Paul D. Losty
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Peter Paul Rickham (1917–2003)

This textbook is dedicated to Peter Paul Rickham, pioneering surgeon, who co-founded the world's First neonatal surgical unit at Alder Hey Children's Hospital Liverpool, United Kingdom.

Foreword

Peter Paul Rickham graduated in medicine from Queens' College, Cambridge, and St Bartholomew's Hospital, London, in 1941. He trained in paediatric surgery at the Hospital for Sick Children, Great Ormond Street, London, under Sir Denis Browne and under Isabella Forshall at Alder Hey Children's Hospital, Liverpool, where he was appointed consultant paediatric surgeon in 1953.

At Alder Hey, Rickham established the hospital as a regional centre for neonatal surgery, he instituted a neonatal transport system for the safe transfer of surgical neonates from a wide area around Liverpool to Alder Hey and he inaugurated the world's first neonatal surgical intensive care unit which was the prototype emulated at centres throughout the world. As a result of the developments, neonatal surgical mortality decreased from 78% to 26% over a period of only 3 years. The subject of his MD thesis was "The Metabolic Response of the Newborn to Surgery".

Rickham remained in Liverpool until 1971 when he was then appointed Professor of Paediatric Surgery at the University Children's Hospital, Zurich, Switzerland, where he remained until retirement in 1983. At Alder Hey he trained numerous surgeons throughout the world particularly from the United States, Japan, Europe, Asia and South Africa.

He was the recipient of many awards and distinctions including the Denis Browne Gold Medal of the British Association of Paediatric Surgeons of which he was founder member and later President, the Legion d'Honneur, France, the Commander Cross, Germany, Ladd Medal Surgical Section of the American Academy of Pediatrics and two Hunterian Professorships from the Royal College of Surgeons of England.

The first edition of *Neonatal Surgery* co-edited with J. Herbert Johnston was published in 1969. It was the first textbook devoted entirely to neonatal surgery based on the accumulating experience of newborn surgery carried out at Alder Hey Children's Hospital from 1953 to 1968. It was, in its time, the "bible" of neonatal surgery and I read it from cover to cover before, during and after my time as a Smith and Nephew Fellow studying under Peter Paul Rickham in 1970. Two subsequent editions of *Neonatal Surgery* were later published in 1978 and 1990. The scope of these publications was expanded, and new contributions from a range of experts of international repute were included.

It is pleasing now to witness a major new international textbook launched from Alder Hey titled *Rickham's Neonatal Surgery* edited by Paul Losty

(Liverpool, UK), Alan Flake (Philadelphia, USA), Risto Rintala (Helsinki, Finland), Naomi Iwai (Kyoto, Japan) and John Hutson (Melbourne, Australia). This new textbook has a truly international list of distinguished contributors covering the full range of neonatal surgical conditions and related topics. Among many key themes comprehensively included in the new book attention also focuses on advances in fetal surgery, minimal invasive surgery, long-term outcomes and evidence-based surgery.

The textbook is a fitting tribute to the life and work of Peter Paul Rickham who was my mentor and good friend.

London, UK Lewis Spitz

Editors' Preface: Rickham's Neonatal Surgery

In 1969, Peter Paul Rickham and Herbert Johnston published the first edition of Neonatal Surgery from Alder Hey Children's Hospital Liverpool which for many paediatric surgeons was considered to be one of the leading textbooks in the world dedicated to newborn surgery. The huge success of the first edition was followed with further editions of this landmark textbook published in 1978 and 1990. Peter Paul Rickham is credited with establishment of the world's first neonatal surgical unit at Alder Hey in 1953 co-founded together with Isabella Forshall. Indeed, it is perhaps then no great surprise that several generations of young paediatric surgeons travelled to Liverpool to work with Rickham and the team of surgical staff based at Alder Hey. Peter Rickham was fortunate to also have Jackson Rees a pioneer in neonatal anaesthesia as a consultant colleague during that era. The "impossible became possible". Many young surgeons who visited Alder Hey later advanced to become world leaders in paediatric surgery across four continents.

This new textbook "Rickham's Neonatal Surgery" is dedicated to Peter Paul Rickham including past and present staff at Alder Hey. The team of editors have assembled leading experts with co-authors to provide state-of-the-art chapters covering the speciality field of neonatal surgery and its related disciplines including fetal medicine, fetal surgery, radiology, newborn anaesthesia, intensive care, neonatal medicine, medical genetics, pathology, cardiac surgery and urology. Contributions from the basic sciences and laboratory research are highlighted in the textbook reflecting steady progress in our current working knowledge and understanding of many neonatal surgical disorders. Evidence-based studies and "best practice" provide the reader wide-ranging information including the latest developments in many chapters. As huge advances have been made in neonatal surgery with improved survival particularly in the past decade(s), ethical issues, long-term outcomes and quality of life are also emphasised by the individual contributors. We hope the textbook will be an authoritative reference for surgical residents in training, consultant surgeons, general surgeons with an interest in paediatric surgery, neonatologists, paediatricians, intensive care specialists and nursing staff. The editors are greatly indebted to the many authors from across the world for their excellent contributions and for some their lifelong professional associations having trained or worked as surgeons at Alder Hey.

Special thanks must go to Barbara Lopez Lucio who worked tirelessly with all authors, editor-in-chief and editorial team to make the project possible. We greatly value and appreciate the skills of the artist(s) and illustrators

for their high-quality work. Finally, enormous gratitude is owed to Julia Megginson, Wyndham Hacket Pain and Melissa Morton at Springer, London, UK, for the final production of the textbook.

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Part I

General

Medical Law as Applied to Neonatal Surgery

1

Robert Wheeler

Abstract

Medical law as applied to neonatal surgery, when considered in terms of the number of requests for legal or ethical opinions, is mainly concerned with the withdrawal or withholding of treatment. However, this must be placed into the context of the chronological opportunities for law to intervene in clinical care. For that reason alone, this chapter commences with the unborn child, passing through the stage of birth, initial decisions on viability (and acquiring a legal parent); before progressing to the 'baby cases', and subsequent guidance when considering the withdrawal of care in neonatal surgery.

Keywords

Ethics • Medical law • Neonatal surgery • Paediatric surgery

Medical law as applied to neonatal surgery, when considered in terms of the number of requests for legal or ethical opinions, is mainly concerned with the withdrawal or withholding of treatment. However, this must be placed into the context of the chronological opportunities for law to intervene in clinical care. For that reason alone, this chapter commences with the unborn child, passing through the stage of birth, initial decisions on viability (and acquiring a legal parent); before progressing to the 'baby cases', and subsequent guidance when considering the withdrawal of care in neonatal surgery.

Contained within a book emerging from one of the founding centres of neonatal surgery in the British Isles, it is unsurprising that this chapter rests squarely on the common law in England and Wales. However the judges creating that law constantly survey the decisions of their colleagues in North America, Canada and Australasia which in turn influences the English decisions. Since the commencement of the Human Rights Act 1998, our courts are also constrained by the European Convention of Human

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Rights, so that the law pertaining to neonatal surgery described in this book is derived from broad international experience.

1.1 Wrongful Birth

International experience is nowhere better reflected than in wrongful birth. This is a topic which mainly relates to foetal medicine, rather than to neonatal surgery. Applicable only to the precursor of the newborn child, it is included for completeness. But many of us provide antenatal counselling to prospective parents, and it is instructive to reflect on the consequences that could, in principle, flow from this.

Parents of children born with an affliction that could and should have been detected in utero have been suing their clinicians for some years. An early case [1] in the New York Court of Appeals found that parents could claim the costs of institutional care of their child who was born with Down's syndrome, following their doctor's failure to recommend amniocentesis to the 37 year old mother. Courts immediately found such cases difficult due to conflicts of interest. There was public policy to consider; of favouring life over abortion; to be weighed against a woman's prerogative of control over her own body. What emerged was a rule accepted in at least 30 US states that valid claims for wrongful birth will succeed [2].

In the United Kingdom, the action is also allowed, with evidence that many are settled without recourse to the courts [3]. Nevertheless, litigation over failure to diagnose a wide field of diseases that are identifiable antenatally, including congenital rubella syndrome, Duchenne muscular dystrophy and Down's syndrome have been reported.

In addition, in a Scottish case [4], a father was been awarded damages for the shock and distress he has suffered as a result of the birth of an affected child. This was unusual, since such damages have usually been limited to the mother, and evidence of psychiatric harm has previously been required. Neither of these applied in McLelland.

1.2 Proposed Guidelines for Instituting Intensive Care at Birth

In a report [5] commissioned by the Nuffield Council on Bioethics, guidelines were proposed for deciding as to whether babies of certain gestational age should have limitations placed on their resuscitation and intensive care. These proposals were based solely on judgement of the best interests of a premature child, irrespective of the wider issue of whether clinical resources were available to support this aspect of neonatal medicine. The working party concluded that below 22 weeks of gestation, no baby should be resuscitated, unless this was taking place within all the safeguards of a clinical research study. For babies between 22 weeks and 22 weeks 6 days of gestation, "…standard practice should be not to resuscitate a baby, (and that) … resuscitation would normally *not* be considered or proposed". In this group, parents' views might lead to a reversal of this approach, after a thorough discussion of the risks and prognosis with an experienced clinician. In babies between 23 weeks 0 days and 23 weeks 6 days, precedence should be given to the views of the babies parents, but there is no clinical obligation to embark on treatment that is 'wholly contrary' to clinical judgment.

This brief description does not do justice to a 250 page report of great quality. However, it is cited as an illustration of the national efforts being made to define some limits to treatment at the commencement of extra-uterine life, based on a balance between the importance of preserving life, whilst at the same time acting a in a child's best interest.

1.3 Parental Responsibility

Parental responsibility is conferred by statute [6] and is defined as 'all the rights, duties, powers, responsibilities and authority which by law, a parent of a child has in relation to the child …. ' Included is the right to provide consent for

treatment where necessary. The child's mother (the woman who gave birth to the baby, rather than the person who provided the egg from which he was conceived, if different) automatically gains parental responsibility. The child's father gains parental responsibility automatically if married at the time of the birth registration. Since 2003, unmarried fathers also get parental responsibility automatically, when they register the birth.

If the father subsequently marries the mother, he acquires parental responsibility, an acquisition described as 'legitimation' [7].

Alternatively, parental responsibility can be acquired by the unmarried father either with the agreement of the child's mother, or by application to a court.

Parental responsibility is passed to adoptive parents on legal adoption. It may be shared with guardians appointed by parents; with local authorities; and is linked to various legal orders [8].

The person with parental responsibility who provides consent for a child's surgery must act in the child's best interests in so doing. These are usually self evident, and the agreement between parents and surgeon is reached after full disclosure of the relevant information.

1.4 The 'Baby Cases'

Medical law is a relatively modern discipline. In some respects, it has been built upon cases considering whether a child with congenital malformations should be treated, or allowed to die without operation. It should be remembered that these 'withdrawal' cases only get to court if there is dissent; between surgeons, physicians, nurses or parents. Provided all agree that withdrawal (or continuation of treatment) is in a baby's best interest, the effects of their joint decision attract no public attention. It is only where one or other group powerfully disagree over the management plan that litigation occurs, and it is helpful to begin with the English cases, in chronological order.

1.4.1 Baby Alexandra, and the Question of Life's Sanctity

In a case known as Re B,[1] the parents of a newborn with Down's syndrome and duodenal atresia wished to allow their child to die, rather than undergo surgery. Her doctors disagreed, and the local authority was given care and control of the baby. The court authorised surgery, but when the child was transferred for operation, the surgeons were unwilling to operate, in view of the parents' objections. The local authority returned to court, but the judge, after hearing the parents' views, withdrew authorisation for the surgery.

The case was then considered by the Court of Appeal, which was told that other surgeons would be prepared to operate. This court found that the judge had placed too much emphasis on the wishes of the parents, and that it was the *best interests* of the child that should prevail. To determine these best interests, the appeal court created a test: Was Alexandra's life "…. demonstrably going to be so awful that in effect she should be condemned to die, or whether the life of this child is still so imponderable that it would be wrong for her to be condemned to die?"

Concluding that the surgery would give her the chance to live the normal life expectancy of a child with Down's syndrome, the court allowed the appeal, and Alexandra's surgery was performed. However, in his leading judgment, Templeman LJ acknowledged that "… there may be cases … of severe proved damage where the future is so certain and where the life of the child is so bound to be full of pain and suffering that the court might be driven to a different conclusion". The court thus established two cornerstones of modern jurisprudence. That there was no absolute parental right to control the fate of a child in these circumstances; and that there was no absolute right to life for a child.

Thus the foundations were laid for the *quality of life* to be used as a yardstick of the success of

[1] Re B (A Minor) (Wardship: Medical Treatment) (1982) FLR 117.

therapy, rather than merely the preservation of life, irrespective of its quality.

Furthermore, the case provided an early example of a balancing exercise that must be employed when determining the best interests of children. Such an exercise is as applicable to surgical decision-making as it is to judicial deliberation.

1.4.2 Dr. Arthur

No account of neonatal law can ignore the case of Dr. Leonard Arthur [9], who was charged (initially) with the murder of a child with Down's syndrome.

It must be understood that this famous case is a legal anomaly. It is a solitary criminal case nestling amongst a group of private civil medical law cases, and the outcome was unexpected.

Dr. Arthur's patient was a baby boy with uncomplicated Down's syndrome who had been rejected by his mother. On the basis that neither parent wished the child to survive, Dr. Arthur prescribed 'nursing care only', together with dihydrocodeine as required, 5 mg four hourly. The child died 2 days after birth; the cause of death being attributed to bronchopneumonia resulting from Down's syndrome.

The prosecution alleged that Dr. Arthur decided to cause the death of the child. The jury disagreed, and acquitted him after 2 h deliberation. A successful conviction had been anticipated. The case caused a furore, commentators roundly criticising [10] the judge's presentation of the legal issues to the jury. In particular, the judge failed to apprise the jury of Dr. Arthur's homicidal intent.

It could be inferred from the facts of the case that Dr. Arthur administered dihydrocodeine in order to end his patient's life. This element of intention to kill is crucial in obtaining a conviction for murder. How Dr. Arthur escaped this remains a matter of speculation amongst lawyers, who almost invariably point out [11] that the case holds no value as a precedent for future decisions.

Dr. Arthur was represented at trial by George Carman QC, the foremost defence counsel of his generation. Controversially, he advised his client *not* to give live evidence at the trial. Carman's biographer [12] reveals that in the barrister's view, "if Leonard Arthur had been asked 'When you decided on the way to treat this baby, what did you intend to happen?', Arthur would have replied 'I intended it to die'. End of story".

The case was therefore highlighted as an anomalous criminal judgement, but together with a reported case a few weeks preceding it [13], (that no action being taken against a doctor who had allegedly refused to sustain a baby with spina bifida), it brought non-treatment of newborns to the public attention. It also caused consternation amongst doctors, (some of whom) failing to appreciate the distinction that was being made between withholding treatment from a dying patient, as opposed to depriving hydration and nutrition from a child who was otherwise healthy. This error was encapsulated in a statement from the President of the Royal College of Physicians: "… I say that with a child suffering from Down's and with a parental wish that it should not survive, it is ethical to terminate life … [14]".

In reality, Dr. Arthur's mistake, in retrospect, was to conflate 'futility' with an obligation to accede to the parents' wishes that their child should not be treated. One of the legal mistakes was to allow the jury to believe that the doctor's duty to a child with Down's syndrome could be different from, and lower than, that owed to a child without the syndrome. That was and is quite wrong. The doctor's obligation is to do what is reasonable in all the circumstances of his or her patient.

1.4.3 Re C, and the Emergence of the Best Interests of the Child

Baby C was born prematurely in 1988 with hydrocephalus; at birth, her doctors considered her to be terminally ill, due to associated cerebral structural damage. However, a shunt was inserted at 2 weeks to prevent enlargement of her head. The question arose as to whether and how she should be treated in the event of shunt blockage,

or infection. It was the disparity of the advice between the local authority's social and legal services that lead to a review of the case in the Court of Appeal [15]. The child's social worker concluded that the doctors should treat C in a way "appropriate to a non-handicapped child". The legal department concluded differently, that C should "… receive treatment as is appropriate to her condition". The leading judge in the Court of Appeal was firmly in agreement with the latter view:

"You do not treat a blind child as if she were sighted, or one with a diseased heart as if she was wholly fit" [16].

The Court of Appeal was careful to issue directions that were not explicit, authorising the hospital "… to treat the minor to allow her life to come to an end peacefully and with dignity".

Re C is the case that Lord Templeman had anticipated during his judgement in Baby Alexandra. Baby C was dying, untreatable, with a quality of life far removed from that which a child with Down's syndrome could reasonably expect. Baby C's physical limitations could be predicted to lead to the demonstrably awful and intolerable life of suffering that Alexandra would hope to avoid.

The decision confirmed that there is no absolute right to life; and the full judgement provides powerful reassurance [17] that English law refuses to countenance killing patients.

1.4.4 Re J, and 'Substituted Judgements'

In the case of a 27 week premature baby [18] with severe brain damage, the question for the court was how the child should be managed in the event of a further collapse. J was born at 1.1 kg, and required ventilation for 4 weeks. Oxygen-dependent for a further 6 weeks, he was discharged home at 3 months of age, but had a cyanotic collapse at home a few days later. This acute illness, which necessitated 3 more weeks of ventilation, caused parenchymal brain damage; the prognosis was of severe spastic quadriplegia.

In an initial approach to the court, following the diagnosis of the brain damage, an order was made that it would not be in J's best interests to reintubate him "unless to do so seemed appropriate given the prevailing situation. If he developed a chest infection treatment with antibiotics and maintenance of hydration was recommended, but not prolonged ventilation" [19].

Representing the public interest, the Official Solicitor appealed this decision, on the grounds that a court was never justified in withholding consent to life-saving treatment to a child, irrespective of the quality of life which it would afterwards experience. The Court of Appeal held that a medical course of action which failed to prevent death could still be in a child's best interests. Furthermore, that there was no absolute rule that, (except when a child was already dying), neither the court nor any responsible parent could approve the withholding of life-saving treatment on the basis of the quality of the child's life". This judgement, and those that preceded it, established a precedent in English law for the withdrawal of treatment on the basis of a poor quality of life.

The court in Re J also reviewed the 'demonstrably so awful' test that had emerged in baby Alexandra's case. There was concern that this test allowed courts to determine the patient's quality of life by their own standards, whilst having no understanding of the situation from the patient's own perspective. Thus, the restrictions that severely disabled people face in their daily activities might not be as incompatible with a rewarding and fulfilling life as many judges might assume.

From this idea flowed the proposal that the anticipated quality of life that the child might have to endure should be judged *from the viewpoint of the child*; as to whether it would be intolerable *for him*.

This is described as the 'substituted judgement' test. The Court thus emphasised that any assessment of the forthcoming quality of life should be made from the assumed view of the child patient, rather than that of the adult decision-maker.

This was a radical view from a legal system based upon judges arriving at their own view of a

child's best interests, and drew wide criticism [20]. Not least, because it involves the creation of a legal fiction: Baby J had no capacity to create a 'viewpoint', so there was no way in which his supposed views could be predicted. Any assumed view would thus be entirely a creature of the judge's imagination. Nevertheless, the substituted judgement was an important milestone in the jurisprudence of withdrawal, and its effects remain visible today.

1.4.5 Re C, and the Reassertion of Parental Rights?

This case from 1996 concerns a baby with biliary atresia [21]. C underwent a Kasai procedure at three and a half weeks, but biliary drainage was not achieved. His parents were influenced by the pain and distress their son experienced in preparation for, and subsequent to, the surgery and resolved that if the Kasai was unsuccessful, they did not wish him to undergo a liver transplant. The clinicians looking after C provided a unanimous prognosis that without transplant, he would die; and thus it was in his best interests to receive a new liver when one became available.

After the failure of the portoenterostomy was recognised, C's parents left the jurisdiction, taking jobs in a distant Commonwealth country. The clinicians, via the local authority, applied to the courts seeking three decisions; (i) whether it was in C's best interests to undergo liver transplantation; (ii) permission to perform transplantation notwithstanding his mothers refusal to consent; (iii) for the child to be returned to England for this purpose. When C was 17 months old, the High Court granted all three requests, ordering his return to this country within 21 days.

C's parents appealed, and the Court of Appeal handed down the judgement 5 weeks later.

This court distinguished C from previous cases, which it asserted had been decided largely upon the *medical* best interests of the children concerned. Butler-Sloss LJ, a judge in the appeal, considered that insufficient emphasis had been given to "the enormous significance of the close attachment between the mother and baby [and whether it was]. .in the best interests of C … to direct the mother to take on this total commitment where she [did] not agree with the course proposed".

The court thus expanded the concept of 'best interests' to incorporate non-medical considerations, such as how a decision might have impact upon the relationship between a child and his parents; and arguably, on the interests of the mother.

The ruling was mainly criticised on this basis; that there was a failure sufficiently to differentiate the interests of the child and his mother … which arguably, could be in conflict. For instance, cases may occur when parents wish to move to a distant country only for reasons of employment … irrespective of the harm to their child, now unable to get access to necessary therapy. Commentators [22] suggest that the emphasis this case gives to (enhanced) parental rights is reminiscent of the situation in England in the nineteenth century. Nevertheless, the case does emphasise the need to consider the wider aspects of a child's best interests when deciding cases of treatment withdrawal.

1.4.6 Re A; Conjoined Twins, and the Impact on the Influence of Parents

In a case [23] from September 2000, the Court of Appeal was faced with the onerous task of balancing the opposing interests of two babies. Born conjoined, these ischiopagus twins shared a common aorta. The court heard that Mary, the weaker child, would die during the proposed separation from Jodie, who was given a good prognosis if separated. The court was also told that if separation was not performed, death of both twins would be inevitable in a matter of months, due to heart failure.

The reason for the approach to court was that the parents of the twins, who were Maltese, were devout Roman Catholics; they were unwilling to provide consent to allow one twin to be sacrificed in order that the other might live.

In this unusual situation, the court had to decide the correct principle to apply when there

was an overt conflict between the rights of the two girls; and between their rights, and those of their parents. Furthermore, the criminal law problem; that Mary's inevitable death would raise the inescapable inference that the surgeons had intended her death.

In respect of the conflicting rights between the babies, the majority of the judges held that their interests should be balanced, and the least detrimental alternative should be chosen. Since surgery would offer Jodie the chance of a relatively normal life, whilst not affecting Mary's fate, the court sanctioned the operation.

Considering the conflict between the interests of the girls and their parents, the court reiterated the principle that the parents' views were not determinative. In doing so, the court rejected the approach in Re C, above. In finding that the parents' religious views were not of decisive importance when considering the jeopardy a child's life, the court reaffirmed the general principle that it is the *child's* welfare that is of paramount importance. Crucially, what the Court of Appeal *did not do* was reject the wider principle in Re C; that evaluation of the child's best interests should not be confined to medical best interests.

In terms of the criminal law, the difficulty of the situation before the court was reflected in the variety of the solutions found to assert that separation, resulting in Mary's death, would be lawful. The judges were searching for a defence to what would otherwise be murder. One judge construed this as a form of self-defence; seeing "… no difference between … resort to legitimate self defence and removing the threat of fatal harm to [Jodie] presented by Mary's draining her life blood".

The court, agonising, concluded that the surgery could lawfully be performed.

In Bainham's words [24], the case:

> "[Is] one rather stark demonstration of the lack of a shared morality about these life and death decisions. For the Roman Catholic parents it was morally wrong to kill Mary. For others it was morally wrong not to bring about her death since there was a moral duty to save Jodie".

This series of cases provides the common law background for our current handling of withdrawal of care in neonatal surgical cases. These, together with statutory and professional influences have provided the principles by which we are guided in clinical practice.

1.5 Statutory Guidance

The Children Act 1989 is the cornerstone of modern children's legislation in England and Wales, and was intent on placing the child's interests, rather than those of the parents, at the centre of decision making. At the opening line of the Children Act 1989 [25] is the *paramountcy* principle:

"When a court determines any question with respect to:

(a) the upbringing of a child … the child's welfare shall be the court's paramount importance"

The Act provides, in addition, for a welfare 'checklist', by which a court must evaluate the effect of any proposed decision that will affect the child. These include:

(a) the ascertainable wishes and feelings of the child concerned (considered in the light of his age and understanding);
(b) his physical, emotional and educational needs;
(c) the likely effect on him of any change in his circumstances;
(d) his age, sex, background and any characteristics of his which the court considers relevant;
(e) any harm which he has suffered, or is at risk of suffering;
(f) how capable each of his parents, and any other person in relation to whom the court considers the question is relevant, is of meeting his needs;
(g) the range of powers available to the court under this Act in the proceedings in question.

It can immediately be seen that not every heading on the checklist is applicable to surgical

babies. But some headings from this checklist form an aide memoire for reminding us all of the matters that we should be considering when we decide whether the clinical management we propose is in the child's best interest; reminiscent of the expansion from solely medical best interests that the court in *Re C* alluded to. It should be emphasised that although the welfare checklist is applicable to withdrawal of treatment (as a "decision that will affect the child"), in the vast majority of cases, the checklist will be employed in lesser decisions.

As an example, faced with the decision as to whether stoma formation is the correct approach in a baby with NEC, the main consideration will undoubtedly be on 'surgical' grounds of safety and efficacy. However, if the result of that initial determination still leaves you in equipoise, the ability of the nurses (or the parents) to manage the stoma; the cultural implications of exteriorised bowel; and the potential problem this may cause with bonding with his parents may also require some thought. In considering these influences, you have adhered to the principles behind the creation of the welfare checklist.

1.6 Practical Application

As neonatal surgeons, we are sometimes faced with a neonate who has lost all the small bowel. It may be instructive to consider how we deal with the next steps, upon this discovery.

It is self evident that it is far better to anticipate such findings, and discuss the ramifications of total gut loss before you start the surgery on their child. Nevertheless, once the diagnosis is made at operation, it is likely that you will need to return to the parents, further to discuss the clinical situation, before making a final decision on treatment. The correct surgical decision will depend on the circumstances, but options such as central venous catheter insertion and long term parental nutrition, or prompt withdrawal of treatment are likely to be discussed.

In reality, if the clinicians (surgeons, neonatologists and nurses) and the parents are all in complete agreement as to the correct next step, the opportunity to embark upon a discussion of ethical or legal principles does not arise. However, any decision to withdraw treatment should be made only after consideration of the relevant guidelines from the Royal College of Paediatrics & Child Health [26].

These are currently undergoing revision, but provide various categories of clinical situations where it may be legal and ethical to consider withholding or withdrawing life sustaining treatment. Included in theses categories is the "No Chance" situation, where treatment will only delay death, and will not alleviate suffering; and the "No purpose" situation, where the degree of mental or physical impairment would be so great that it would be unreasonable to expect the patient to bear it.

Originally designed to assist clinicians' categorise and thus better understand the wide variety of case they face, these guidelines now begin to feel outdated, hence their revision.

It is to be expected that any unanimous decision will coincide with the best interests of the child, her welfare being paramount, and this will be enacted.

It is only when there is disagreement, with any one of these four parties failing to support the clinical decision, that further exploration of ethics and law may have to begin. In some circumstances, the disagreement is based upon an incorrect belief; and a full discussion between clinical staff and the parents may resolve this.

If the disagreement is based on fundamental differences over the child's prognosis, or over which treatment most closely corresponds with the patient's best interests, it is prudent to obtain an early second clinical opinion. This may be from within the unit, or from an adjacent hospital. If the second opinion does not resolve the disagreement, an opinion from the local clinical ethics committee (CEC) may be helpful, if only to clarify precisely the grounds of conflict.

A member of the CEC may be able to identify options that the clinicians, or parents, regard as sufficiently common ground to allow resolution of the conflict. Even if this is not achieved, a formal review by the CEC will be construed as an important and necessary step, should review by a

court later become necessary. Further consideration by experts within speciality organisations or Royal Colleges may also aid resolution. However, experience indicates that in situations where the CEC review fails to resolve the disagreement, the intervention of a court is likely to become necessary.

This is surprisingly easy to arrange, using the Trust solicitor as a starting point, to clarify the question(s) that the court is asked to decide. Referral to a court should not be seen as a failure. The court is simply another form of second opinion, and its decision will usually be welcomed by those on both sides of the disagreement, since this will bring certainty to the next clinical step, both for clinicians and parents. It should be noted that courts in England and Wales will not usually insist that any identified clinician follows a particular course of treatment. The court merely identifies the child's best interests, and clarifies what further steps would be lawful. If the judgement prescribes treatment that doctors are unwilling to provide on clinical grounds, their obligation will be to refer the patient to a centre that may be prepared to embark on the proposed treatment, and maintain the patient's condition until a transfer can be achieved.

It should be noted that referral to the medical defence organisations is not advocated in this process, since these bodies exist to promote the interests of the doctors, rather than those of the patients. It is submitted that the mechanism described will cater thoroughly for the needs of the neonatal surgical patient; if you feel that recourse to your defence body is prudent, that is clearly a matter for you.

In summary, the common law has provided us with clear guidance in resolving some of the dilemmas in caring for neonatal surgical patients, and this is strongly reinforced by statutory guidance, identifying the child's best interests as paramount.

It will rarely be possible (or proper) to solve dilemmas of treatment limitation without first establishing a broad consensus of opinion that includes those of the baby's parents. In the absence of such unanimity, recourse to the courts for a 'second opinion' will usually be of great assistance, and should be viewed as a positive step.

Conclude … the courts may have an increasing role in resolving these uncertainties.

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Embryology of Surgical Birth Defects

2

Dietrich Kluth and Roman Metzger

Abstract

Today, the embryology of numerous congenital anomalies in humans is still a matter of speculation. This is due to a number of reasons which include:

- Misconceptions and/or outdated theories concerning normal and abnormal embryology.
- A shortage of study material (both normal and abnormal embryos).
- A shortage of explanatory images of embryos and developing embryonic organs.
- Difficulties in the interpretation of serial sections.

In recent years, a number of animal models have been established which helped to overcome the shortage of both, normal and abnormal embryos. However, a general agreement on when, why and how abnormal development takes place, still does not exist. As a result, many typical malformations are still not explained satisfactorily and pediatric surgeons of all specialties are still confused when they are confronted with the background of normal and abnormal embryologic development.

Keywords

Human birth defects • Animal models • Teratology • Human embryology

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2.1 General Remarks on Embryology and The Embryology of Malformations

Today, the embryology of numerous congenital anomalies in humans is still a matter of speculation. This is due to a number of reasons which include:

- Misconceptions and/or outdated theories concerning normal and abnormal embryology.
- A shortage of study material (both normal and abnormal embryos).
- A shortage of explanatory images of embryos and developing embryonic organs.
- Difficulties in the interpretation of serial sections.

In recent years, a number of animal models had been established which helped to overcome the shortage of both, normal and abnormal embryos. However, a general agreement on when, why and how abnormal development takes place, still does not exist. As a result, many typical malformations are still not explained satisfactorily and pediatric surgeons of all specialties are still confused when they are confronted with the background of normal and abnormal embryologic development.

Our understanding of the normal and abnormal development of embryos is still influenced by two theories:

- The 'biogenetic law' after HAECKEL [1].
- The theory of 'Hemmungsmissbildungen' [2].

According to Haeckel's 'biogenetic law', a human embryo recapitulates in its individual development (ontogeny) the morphology observed in all life-forms (phylogeny). This means that during its development an advanced species (a human embryo) seems to pass through stages represented by adult organisms of more primitive species [3]. This theory has been used to 'bridge' gaps in the understanding of normal embryonic development and still has an impact on the nomenclature of embryonic organs. This explains why human embryos have 'cloacas' like adult birds and 'branchial' clefts like adult fish.

The term 'Hemmungsmißbildung' stands for the theory that malformations actually represent 'frozen' stages of normal embryonic development. This theory too has been used to 'bridge' gaps in the understanding of normal embryonic development in a manner which could best describe as 'reversed embryology'. As a result, our knowledge of normal embryology stems more from pathological-anatomic interpretations of observed malformations than from proper embryological studies. The theory of the 'rotation of the gut' as a step in normal development is a perfect example for this misconception [4]. Others are: 'failed fusion of the urethral folds' [5], 'failed closure of the pleuro-peritoneal canals' (congenital diaphragmatic hernia [6],) or 'persistent cloaca' [7].

Today, a growing number of animal models exists which allows embryological studies in various embryological fields. This includes studies in normal as well as in abnormal embryos. Especially for the studies of esophageal and anorectal malformations, a number of animal models had been established.

Advanced technology in a number of fields gives much better insights into human development. This includes ultra sonography of fetuses as well as magnetic resonance imaging (MRI). For detailed embryological studies, scanning electron microscopy is still a very useful tool. STEDING published a scanning electron microscopic atlas of human embryos which provides detailed insights into normal human embryology [8]. Scanning electron microscopy is the perfect tool to document embryonic structures:

- Serial sectioning of embryos and time-consuming three-dimensional reconstructions are not necessary.
- The embryo can be studied in all three dimensions 'on-line'.
- The images and photographs are of superior quality (Fig. 2.1).

Although a number of specific tasks demand the serial section of embryos, the difficulties in the interpretation must not be underestimated. Three dimensional (3D) reconstructions, although feasi-

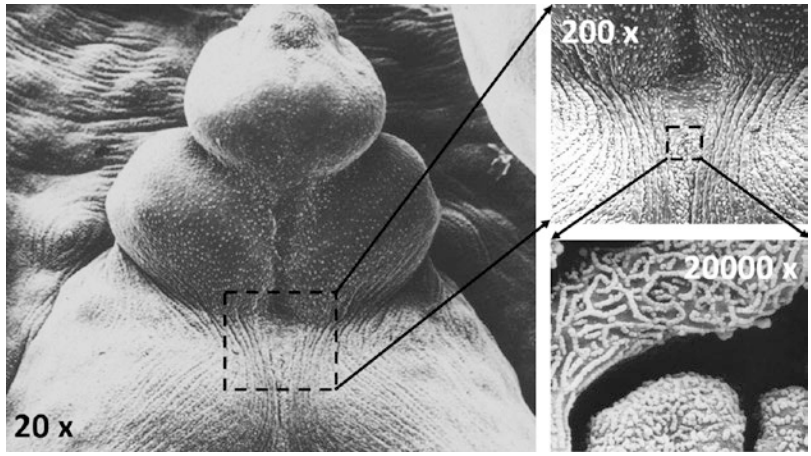


Fig. 2.1 Scanning electron microscopy (SEM) enables a wide range of magnification and a superior quality of photographs: Perineal region of a female rat, ED 20. The highest magnification shows detailed structures on the cell surface. SEM Picture © D. Kluth

ble, are tainted with a loss of information, not only caused by the sectioning itself but also by the use of 3D image software.

2.2 Animal Models Used for Applied Embyology

Over the last two decades a number of animal models had been developed with the potential to gain a better understanding of the morphology of not only of malformed but also of normal embryos. These annual models can be grouped in 5 subgroups:

(a) Embryos of different species for the study of normal embryology.
(b) Surgical models.
(c) Chemical models.
(d) Genetic models.
(e) 'Spontaneous' malformations of unclear cause.

Human embryos are rare. Human embryos displaying typical anomalies are extremely rare. Therefore, it makes sense to study specific developmental processes in embryos of animals with human like abnormalities. However, in all cases of animal models, the detailed study of normal embryos of the same species is mandatory.

We used scanning electron microscopy (SEM) in chicken, rat and murine embryos in order to study certain embryological processes of the normal embryology of the foregut, the hindgut, the midgut, the testicular descent and the development of the external genitalia. The advantage of chicken embryos is the high availability at low costs. They are easily accessible in the eggshell and further breeding is possible when the eggs are treated accordingly. Embryos of rats and mice can be obtained in comparable large numbers; however, local regulations may limit the usage of mammalian embryos.

- The chicken embryo was used to study fore gut development. The aim was to clarify weather lateral ridges occur in the developing foregut or not and, when present, if they fuse to form the trachea-esophageal septum [9, 10].
- Rat embryos were used to study i.e. developmental processes during testicular descent [11], to clarify if 'rotation' takes place during gut development [12, 13] (Fig. 2.2a), to assess the question if 'cloacas' actually exist in rat embryos and how the differentiation of the developing hindgut takes place [12, 13] (Fig. 2.2b).
- Mouse embryos where studied in the SD-mouse model (Fig. 2.3). Here, normal and abnormal hindgut development was studied [14].

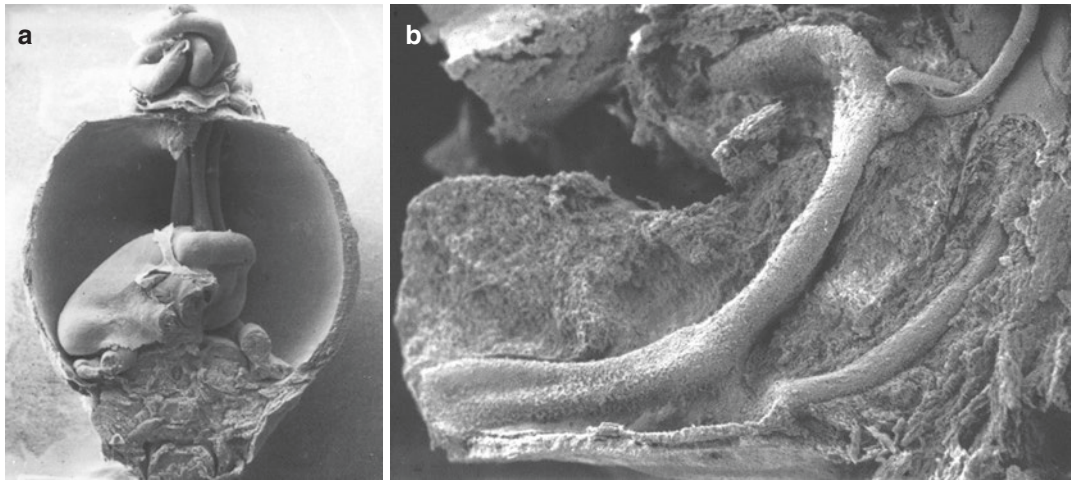
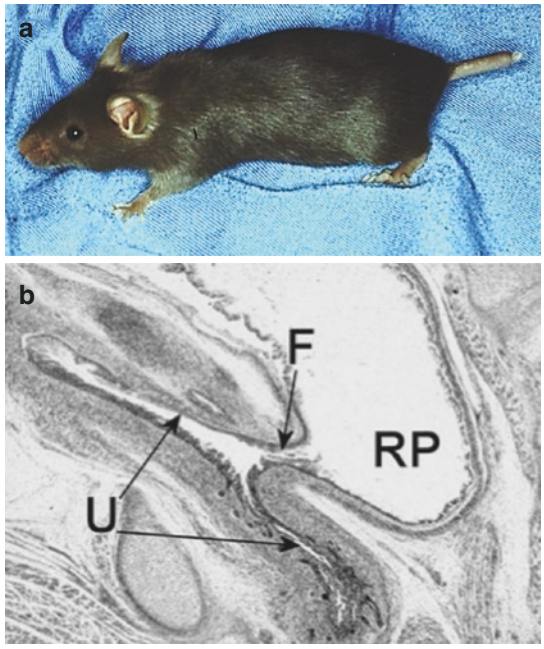


Fig. 2.2 Animal models: Rat embryos were used to study midgut development (**a**) and hindgut development (**b**). SEM Pictures © Dietrich Kluth



c

Anorectal malformations in Sd-mice

	Sd/Sd (n=25)	Sd/+ (n=20)
malformed	24	10
extreme malform.	7	0
recto-ves.fistula	10	1
cloaca	7	4
recto-urethral fistula	0	5
normal	0	8
not documented	1	2

Fig. 2.3 Animal models: SD-mice were used to study ano-rectal malformations. (**a**) Notice the short tail in a heterocygotic SD mouse. (**b**) Histology of the pelvic organs in a newborn heterozygous SD-mouse. The features of an anorectal malformation with recto-urethral fistula (F) and a blind ending rectal pouch (RP) are detectable. *U* urethra. (**c**) The spectrum of malformations seen in SD-Mice. Picture © Dietrich Kluth

In the past, the chicken was an important surgical model to study embryological processes. As mentioned above, the easy access to the embryo, its broad availability and its cheapness makes it an ideal model for experimental studies. It has been widely used by embryologist especially in the field of epithelial/mesenchymal interactions [15–17]. Pediatric surgeons have used this model to study morphological processes involved in intestinal atresia formation [18, 19], gastroschisis [20] and Hirschsprung's disease [21]. The Czech embryologist LAMEZ [22] used chicken embryos in order to induce tracheal agenesis with tracheo-esophageal fistula (Fig. 2.4).

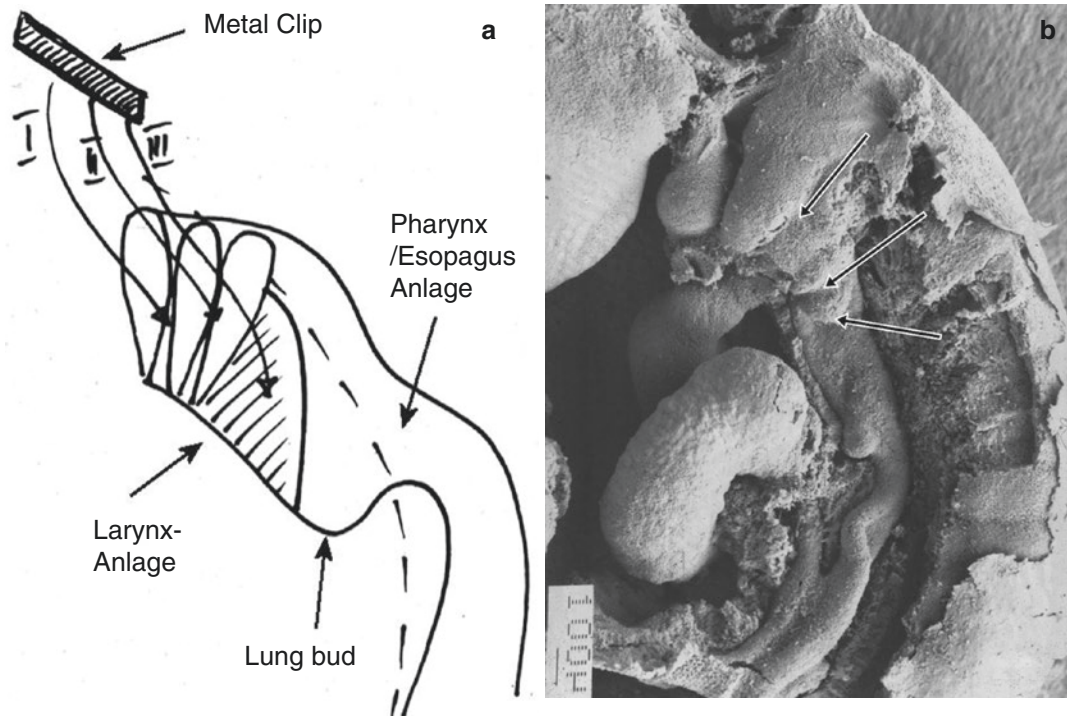


Fig. 2.4 Animal models: Experimental embryology in chicken embryos. Metal clips were used to induce tracheal atresia 18. (**a**) Schematic drawing of the technique, (**b**) arrows indicate the area were the clips were positioned (SEM picture of a chicken embryo). SEM Picture and schematic drawing © Dietrich Kluth

Apart from these purely embryonic models, a large number of fetal models had been developed in the last 30 years. Although they were mainly created to study the feasibility of fetal interventions [23], they also added to our current knowledge of normal and abnormal fetal development and fetal organ systems.

It is well known that a number of chemicals (drugs, chemical fertilizers) can alter normal development of humans and animals alike. Some of these had been used to induce malformations similar to those found in humans. Most important are today:

(a) Adriamycin [24–26]
(b) Etretinate [27, 28]
(c) All-trans retinoic acid (ATRA) [29–31]
(d) Ethylenethiourea [32, 33]
(e) Nitrofen [34–38]
(f) Suramin and Trypan [39, 40]

Models (a-d) have been used to study atresia formation in the esophagus, the midgut and the anorectum. Model (e) was developed to study malformations of the diaphragm, the lungs, the heart and kidneys (hydronephrosis). Model (f) was used in chicken embryos to study the formation of cloacal extrophies.

We used the nitrofen model to study the morphology of diaphragmatic hernia formation in rat embryos (Fig. 2.5).

Many aspects make genetic models the ideal model for the studies of abnormal development. In the past a number of genetic models had been used for embryological studies of malformations. While older models were mostly the product of spontaneous mutations, newer models are, in most instances, the result of genetic manipulations mainly in mice (transgenic mice). The following models had been used by pediatric surgeons:

(a) Models of spontaneous origin: The SD-mouse model [41, 42]. In the SD-mouse model ano-rectal malformations are combined with anomalies of the kidneys, the spine and the external genitalia (Fig. 2.3).

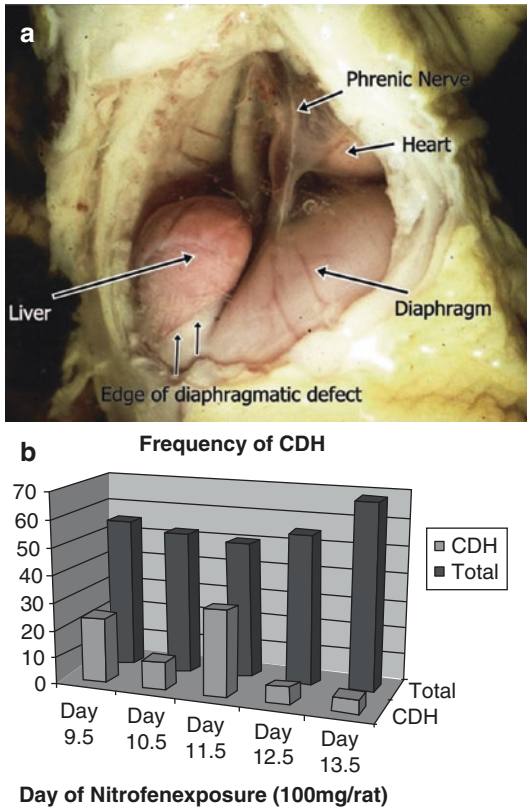


Fig. 2.5 Animal models: The nitrofen model of diaphragmatic hernia. (**a**) Newborn rat with diaphragmatic hernia after nitrofen exposure at day 11.5. (**b**) Results of nitrofen exposure on days 9.5, 10.5, 11.5, 12.5 and 13.5. Most hernias were seen after nitrofen exposure on day 11.5. Picture © Dietrich Kluth

(b) Inheritance models: the pig model of anal atresia [43, 44]. In pigs, ano-rectal malformations are seen quite frequently. One out of 300 newborn piglets present with ano-rectal malformations without evidence of genetical alterations.
(c) 'Knock-out' models.
(d) Viral models.

The number of transgenic animal models is currently growing fast. For pediatric surgeons those models are of major importance, which result in abnormalities of the fore- and hindgut. Here, interference with the Sonic hedgehog (Shh) pathway has proven to be very effective [45–47]. There are two ways to interfere with that pathway:

- Targeted deletion of Sonic hedgehog [45, 46].
- Deletion of one of the three transcription factors Glil, Gli2 and Gli3 [46, 47].

It has been demonstrated, that targeted deletion of Sonic hedgehog resulted in homozygous Shh null mutant mice in the formation of foregut malformations like esophageal atresia/stenosis, tracheo-esophageal fistulas, and tracheal/lung anomalies [48]. In the hindgut, the deletion of Sonic hedgehog caused the formation of 'cloacas' [46], while Gli2 mutant mice presented with the 'classic' form of anorectal malformations and Gli3 mutants showed minor forms like anal stenosis [46, 47]. Interestingly, the morphology of Gli2 mutant mice embryos resembles that of heterocygous SD-mice embryos while Shh null mutant mice embryos had morphological similarities with homocygous SD-mice embryos. It is interesting to note that after administration of adriamycin abnormal pattern of Shh distribution could be demonstrated in the developing foregut [48].

Recently, BOTHAM et al. studied developmental disorders of the duodenum in mutations of the fibroblast growth factor receptor 2 gene (*Fgfr2IIIb*) [49]. They noted an increased apoptotic activity in the duodenal epithelium of *Fgfr2IIIb −/−* embryos at day 10.5, followed by a disappearance of the endoderm at day 11.5. Interestingly, the duodenal mesoderm also disappeared within 2 days and an atresia was formed. Similar processes had been observed in newborn piglets whose esophageal epithelium was removed via endoscopy [50, 51]. This procedure resulted in esophageal atresias in these piglets.

In humans, viral infections are known to cause malformations. Animal models that use viral infections important for pediatric surgeons are very rare. One exception is the murine model of extra hepatic biliary atresia (EHBA) [52]. In this model, newborn Balb/c mice are infected with rhesus rotavirus group A45. As a result, the full spectrum of EHBA develops as it is seen in newborn with this disease. However, this model is not a model to mimic failed embryology. But it highlights the possibility that malformations are not caused by embryonic disorders but caused by fetal or even postnatal catastrophes.

In chicken embryos, a number of spontaneous malformations can be observed. It is not quite clear which processes cause them. One reason may be a prolonged storage (more than 3 days) in fridges below 8° C before breeding is started [53].

Spontaneous malformations of the head anlage (i.e. double anlage of the head), the anlage of the heart as well as abnormalities of the embryonic position (hererotaxia) are frequently seen [53].

This part on embryology and animal models highlights not only the importance to study embryos with experimental malformations but also the study of normal animal embryos. Today, much information in current textbooks on human embryology stems actually from studies done in animals of varies species. Many of these are outdated. The wide use of transgenic mice in order to mimic congenital malformations makes morphological studies of the organ systems in normal mice mandatory. Otherwise the interpretation of the effects by deletion of genetic information can be very difficult or even misleading.

2.3 Scanning Electron Microscopic Atlas of Normal and Abnormal Development in Embryos

In this section we want to present examples of normal and abnormal development as we have seen them in our studies in our labs over the past 30 years using scanning electron microscopy (SEM). We use the form of an embryological atlas following the old motto 'A picture says more than a thousand words'. We focus on the following developmental processes:

- Normal and abnormal foregut development (chicken embryos).
- Normal and abnormal development of the diaphragm (rat embryos).
- Development of the midgut (rat embryos).
- Normal and abnormal development of the hindgut (mice and rats).
- The development of the external genitalia and the urethra (rat embryos).
- Testicular descent (rat embryos).

2.3.1 Normal Foregut Development

Traditionally, foregut malformations like esophageal atresias and trachea-esophageal fistulas are explained by a faulty formation of the so-called 'tracheo-esophageal septum'. It is believed that normal septation takes place in two steps:

1. Lateral endodermal ridges appear in the primitive foregut which fuse and form the trachea-esophageal septum.
2. This solid endodermal septum is partly removed by apoptosis and substituted by mesenchymal cells.

This theory had been described in detail by ROSENTHAL [54] and SMITH [55]. However, neither ZAW TUN [56] nor O'RAHILLY and MÜLLER [57] were able to confirm these sequences of embryological events. According to them, the term 'separation' is a misnomer as the formation of the trachea is simply the result of the down growth of the respiratory diverticulum [58].

Using SEM, we studied the normal development of the foregut in chicken embryos [9, 19, 59].

The first goal of these studies was to see if lateral endodermal ridges appear inside the foregut and if they fuse (Fig. 2.6). However, in our studies we were unable to identify ridges in the lateral foregut wall. Furthermore, signs of fusions of lateral foregut components were also not seen. As no signs of fusion can be demonstrated in the foregut, theories dealing with improper formations of the trachea-esophageal septum are obsolete [56].

The second goal was to visualize the early formation of the lung bud (Fig. 2.7). In our series of embryos we could demonstrate that after the formation of the early lung anlage two lung buds appear, which are the forerunners of the bronchi. The anlage of the trachea itself is seen later as the floor of a 'common foregut' chamber [10]. Thus, not the trachea but the bronchi are the first organs of the respiratory tree that develop. This speaks against the idea of a simple down growth of the tracheal anlage as assumed by ZAW TUN and O'RAHILLY and MÜLLER [56, 57].

The third goal was to identify possible mechanisms of differentiation of the foregut into larynx, pharynx, trachea and esophagus. In our embryos, we could identify typical markers in the foregut (Fig. 2.8). In the dorsal aspect of the foregut a fold appears which

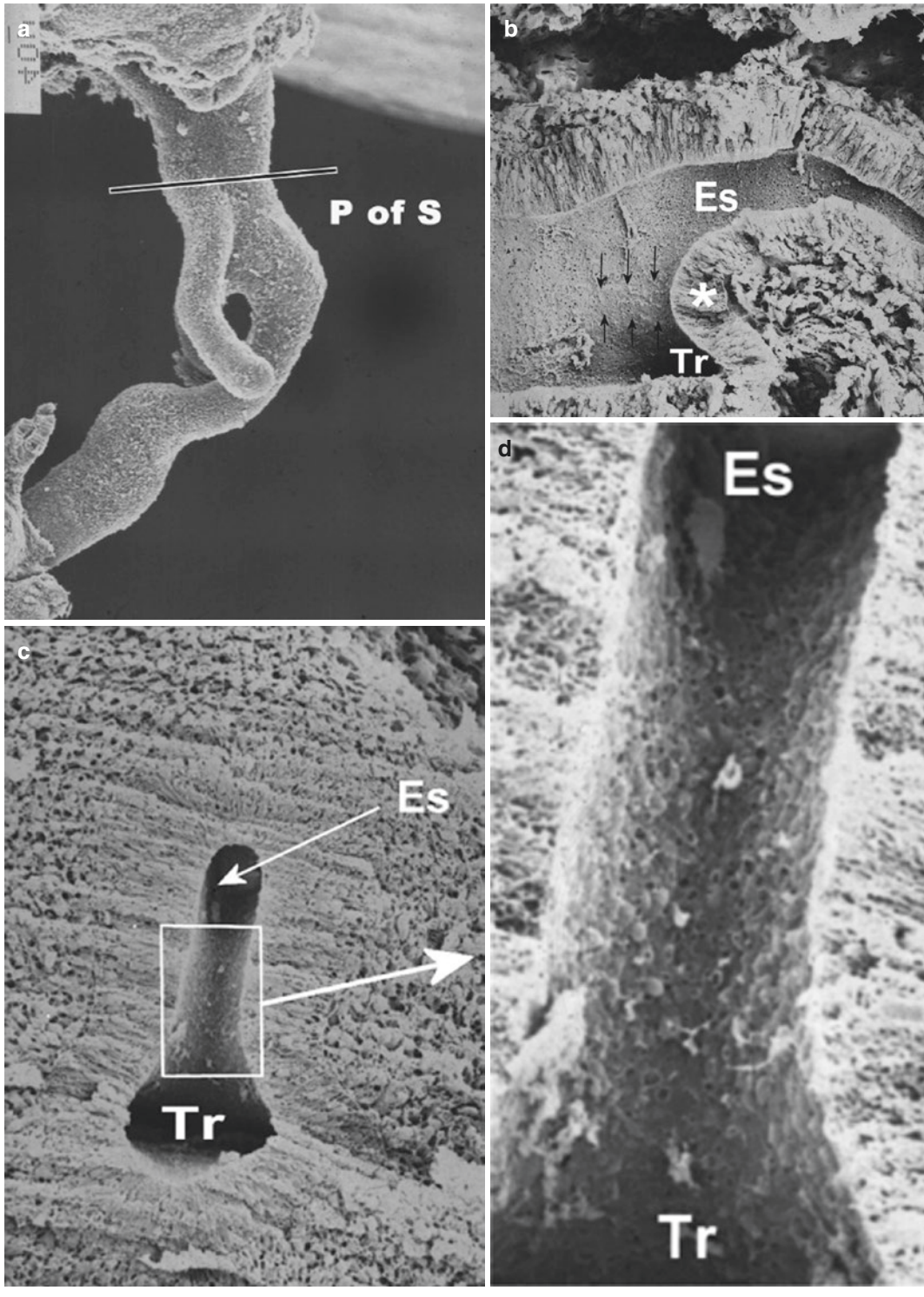


Fig. 2.6 Embryology of the esophagus: SEM studies in chicken embryos. (**a**) Foregut of a chicken embryo of stage20/21, 3.5 days old. (**b**) The foregut is opened from lateral. The inner surface of the foregut is seen. Notice the absence of lateral folds (*arrows*). *ES* esophagus, *TR* trachea, *Asterisk* (*) tip of the trachea-esophageal fold. (**c**) View into the foregut from cranial. The tip of the trachea-esophageal fold can be seen. Notice the absence of fusion (higher magnification in D). *ES* esophagus, *TR* trachea. SEM Pictures © Dietrich Kluth

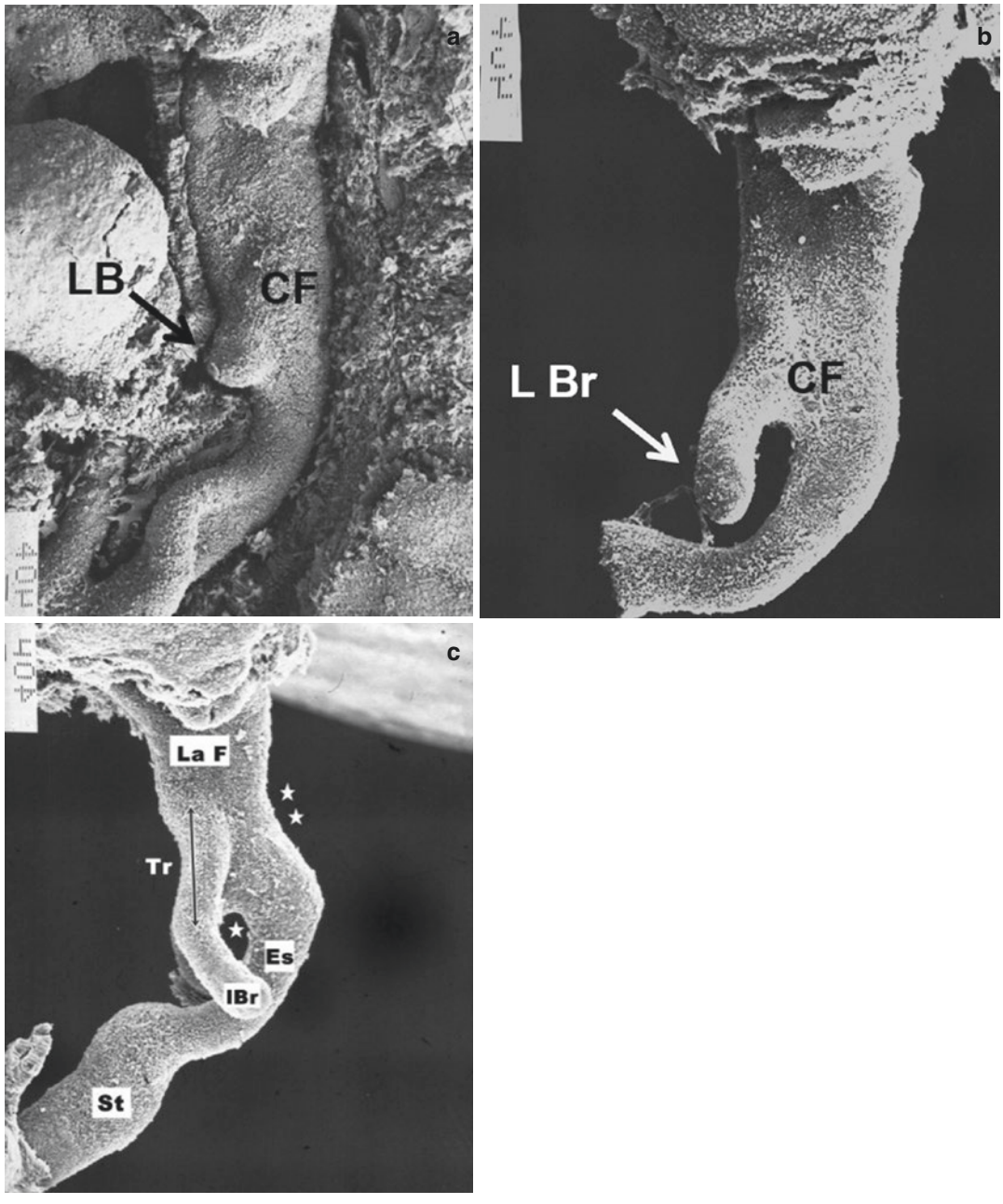


Fig. 2.7 Embryology of the esophagus: Formation of the respiratory tract. (**a**) Lung buds are the forerunners of the bronchi (LB). *CF* common space of foregut. (**b**) The bronchi start to develop (L Br). A trachea is not visible yet. *CF* common space of foregut. (**c**) The trachea (Tr) is still part of the common foregut. *LaF* larynxanlage, *ES* esophagus, *L Br* bronchi, *St* stomach, *Double Asterisk* fold which marks the border between pharynx and esophagus. SEM Pictures © Dietrich Kluth

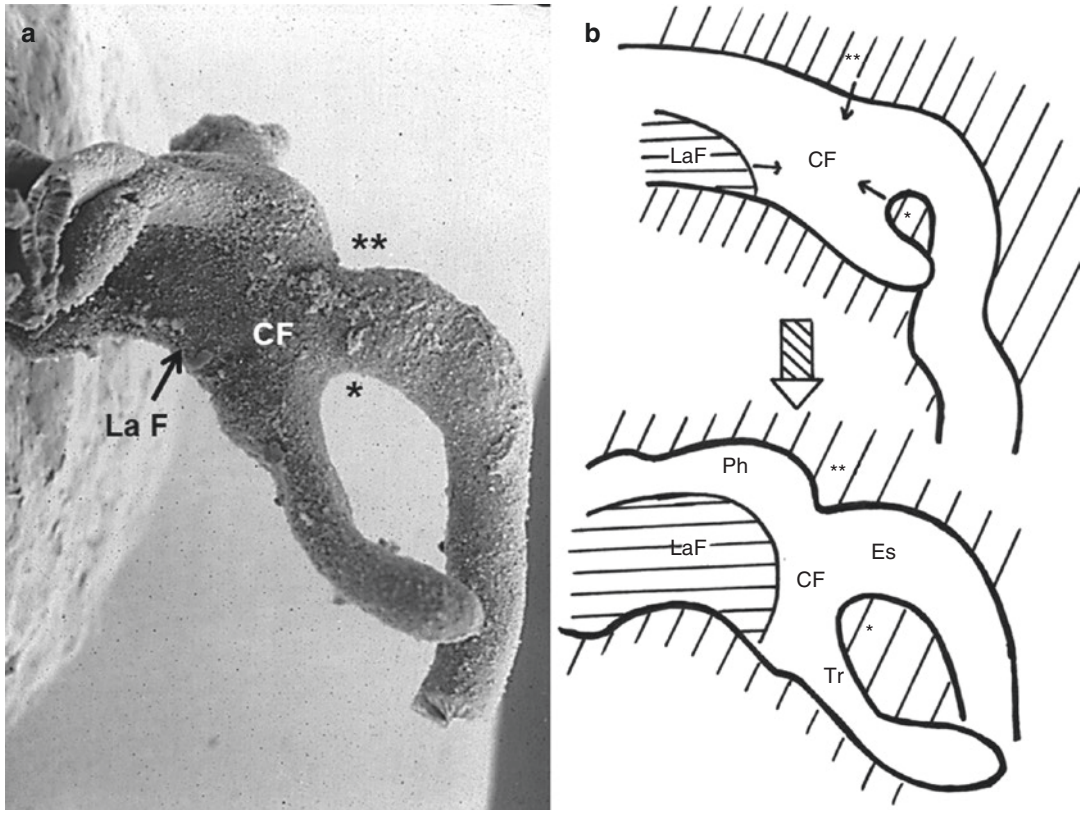


Fig. 2.8 Embryology of the esophagus: The common space of the foregut is reduced in size by a system of folds. (**a**) The trachea is still part of the common space (CF). *LaF* Larynxanlage. (**b**) The size of the common foregut (CF) is reduced by the growth of folds, which are formed by the larynx fold (LaF) from cranial, the trachea-esophageal fold (*asterisk*) from caudal, and the fold between phayrynx and esophagus (*double asterisk*) from dorsal. SEM Picture and schematic drawing © Dietrich Kluth

marks the borderline between pharynx and esophagus. Cranially the larynx develops and caudally, a fold appears between the developing trachea and the esophagus. In the next developmental steps these folds approach each other but do not fuse. As a result, the area of the common foregut is reduced in size and later forms the pharyngo-tracheal canal [5].

2.3.2 The Formation of Esophageal Atresia

Although a number of models for abnormal foregut development exist, a clear morphological description of the embryological events that finally lead to esophageal atresias, are still missing. Based on our observations, the development of the malformation can be explained by disorders either of the formation of the folds or of their developmental movements [9, 10, 59]:

- Atresia of the esophagus with fistula (Fig. 2.9c1):
- The dorsal fold of the foregut bends too far ventrally. As a result the descent of the larynx is blocked. Therefore the common tracheo-esophageal space remains partly undivided and lies in a ventral position. Due to this ventral position the common space differentiates into trachea.
- Atresia of the trachea with fistula (Fig. 2.9c2):

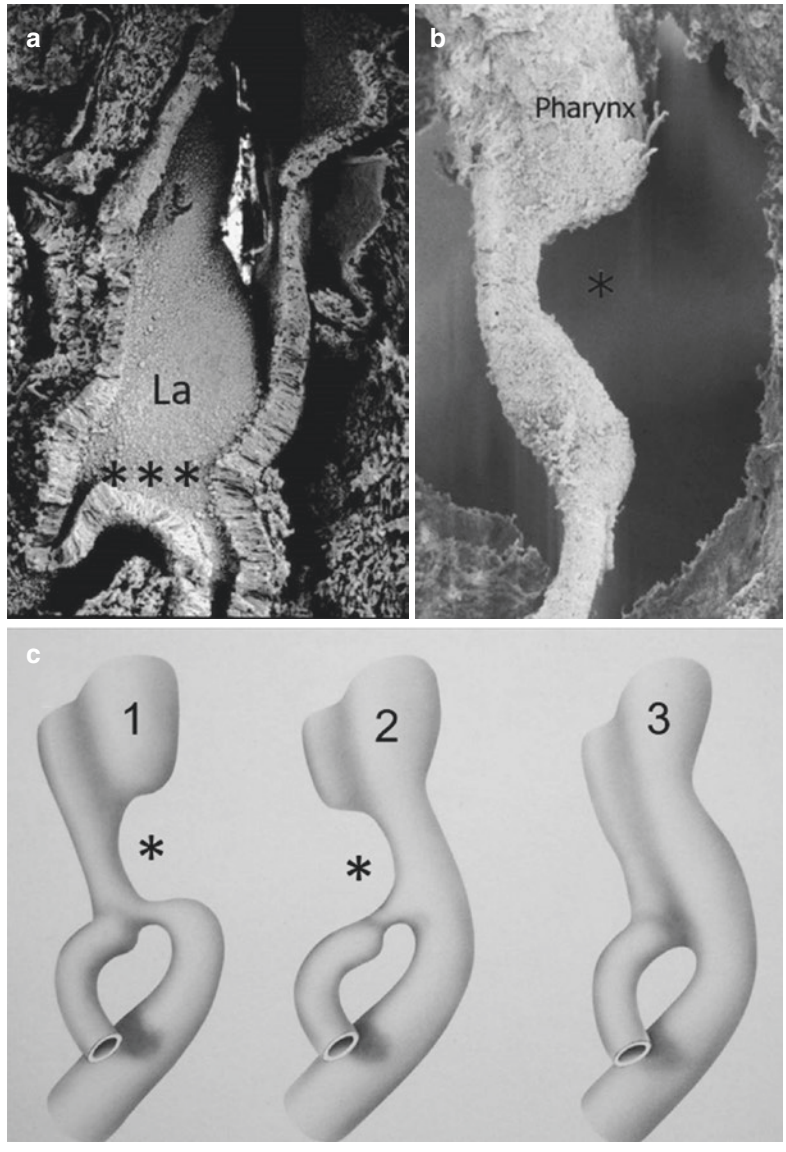


Fig. 2.9 Embryology of the esophagus: Hypothetical formation of foregut malformations. (**a**) Normal foregut of a chicken embryo, view from lateral into the foregut. Notice the reduced size of the common foregut space (*Triple Asterisk*) due to the development of the folds. *La* Larynx. (**b**) Chicken embryo with a spontaneous foregut malformation. The Pharynx ends blindly. Part of the trachea is in normal position and of tracheal size. The dorsal part of the common foregut space is missing (*Asterisk*). (**c**) Hypothetical explanation of foregut maldevelopment. (C1) The dorsal fold (*Asterisk*) between pharynx and larynx grows too deep into the common foregut space. Consequently the rest of the common space develops into trachea and an esophageal atresia with lower fistula develops. (C2) The common foregut space is reduced in size from ventral (*Asterisk*). Consequently the rest of the common space develops into esophagus and a tracheal atresia with fistula occurs (very rare). (C3) Impaired development of the dorsal fold and the tracheo-esophageal fold leads to an undivided common foregut space and a laryngo-tracheo-esophageal cleft. SEM Pictures and schematic drawing © Dietrich Kluth

- The foregut is deformed on its ventral side. The developmental movements of the folds are disturbed and the tracheo-esophageal space is dislocated in a dorsal direction, where it differentiates into esophagus.
- Laryngo-tracheo-esophageal clefts (Fig. 2.9c3): Faulty growth of the folds results in the persistence of the primitive tracheo-esophageal space.

In our collection of chicken embryos we came across an embryo with abnormal foregut features (Fig. 2.9b). When compared to normal embryos of the same age group (Fig. 2.9a), the following statements can be made: (a) obviously, the pharynx ends blindly. (b) The dorsal part of the common foregut space is missing. (c) the ventral part of the common space has the size of a trachea. (d) This foregut looks like the hypothetical form C1 in Fig. 2.9.

2.3.3 Normal Diaphragmatic Development

The traditional theories of diaphragmatic development have been summarized by KLUTH et al. [60]. Using SEM, we have recently restudied the diaphragmatic development. For practical reasons, it is essential to note that the early diaphragm consists of two parts:

- The septum transversum which, in young embryos, is identical to the floor of the pericardium.
- The structures that surround the pleural cavity. They are:
  - The Post Hepatic Mesenchymal Plate (PHMP) [38], which covers the dorsal aspect of the liver and is in continuity to the septum transversum ventrally and cranially.
  - The pleoro-peritoneal fold (PPF) which separates the pleura from the peritoneal cavity. This fold connects ventrally to the septum transversum and the PHMP and dorsally to the mesonephric ridge [61]. This PPF is a structure that is identical to the pleuro-peritoneal membrane of the old literature [60].
  - The dorsal mediastinum which contains the esophagus, the trachea and the Aorta.

According to our SEM studies, the PHMP plays the most important role in normal diaphragmatic development. In Figs. 2.10 and 2.11 the closure process of the pleuro-peritoneal openings (PPO) is depicted. At embryonic day (ED) 13,

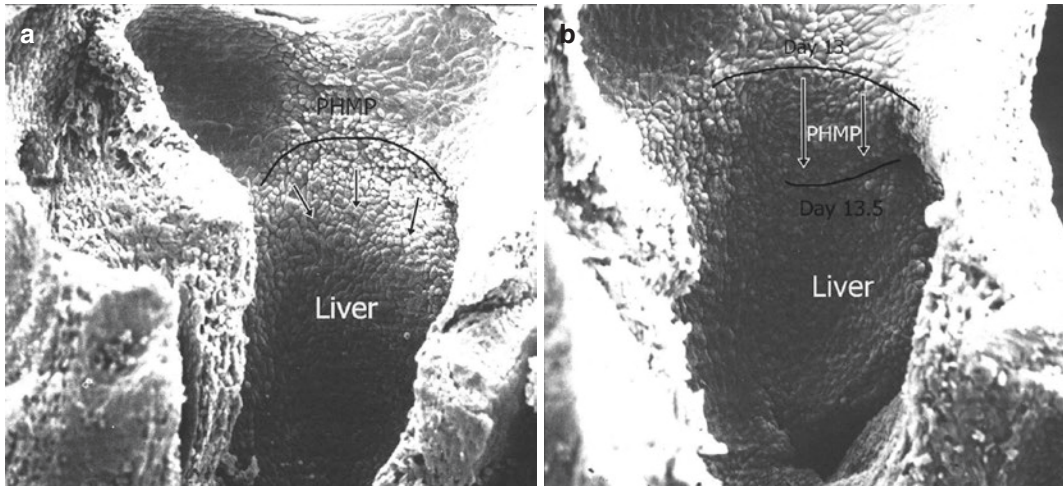


Fig. 2.10 Normal development of the diaphragm: Caudal growth of the posthepatic mesenchymal plate (PHMP) [38]. (**a**) Rat embryo, ED 13. View at the dorsal part of the diaphragm. The dorsal diaphragm is short. The black line in marks the caudal border of the PHMP. Arrows indicate the direction of future PHMP growth. Note the large area of liver still uncovered by the PHMP. (**b**) Rat embryo 13.5 days. Note the caudal growth of the PHMP within 12 h (second dark line). The uncovered liver is markedly smaller. SEM Pictures © Dietrich Kluth

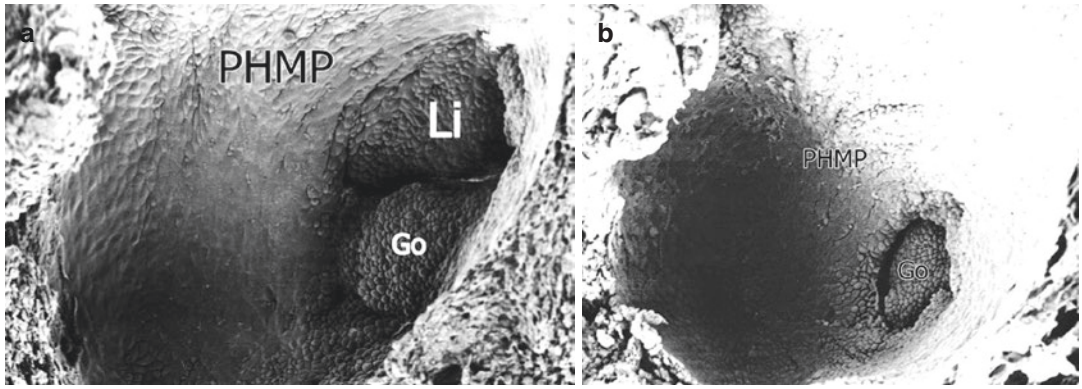


Fig. 2.11 Normal development of the diaphragm: Closure of the pleuroperitoneal openings (PPO). Rat ED 15 (**a**) and ED 16 (**b**). Most of the liver (Li) is covered by the posthepatic mesenchymal plate (PHMP). At ED 16 the only intra-abdominal organ seen is the tip of the gonads (Go). SEM Pictures © Dietrich Kluth

the formation of the PHMP and its lower border can be seen (Fig. 2.10a). The PHMP then expands dorso-laterally at embryonic day 13.5 (Fig. 2.10b), establishing a new lower border.

In Fig. 2.11 the final closure of the PPO is shown. In this process the PHMP starts to cover the last free areas of the liver (Fig. 2.11b). In this process, the PPF plays only a minor role.

In the literature, the nomenclature of the various parts of the diaphragm is confusing. We use the term PPF for a structure which was formally known as pleuro-peritoneal membrane [60, 61]. The term PPF is used differently by GREER and co-workers [62]. Their PPF is very similar to the PHMP as described by IRITANI and us but seems to include the ventral part of our PPF.

2.3.4 Abnormal Diaphragmatic Development

In the past, several theories were proposed to explain the appearance of postero-lateral diaphragmatic defects:

- Defects caused by improper development of the pleuro-peritoneal membrane [63, 64]
- Failure of muscularization of the lumbocostal trigone and pleuro-peritoneal canal, resulting in a 'weak' part of the diaphragm [64, 65]
- Pushing of intestine through postero-lateral part (foramen of Bochdalek) of the diaphragm [66]
- Premature return of the intestines into the abdominal cavity with the canal still open [64, 65]
- Abnormal persistence of lung in the pleuro-peritoneal canal, preventing proper closure of the canal [67]
- Abnormal development of the early lung and posthepatic mesenchyme, causing non-closure of pleuro-peritoneal canals [38]

Of these theories, failure of the pleuro-peritoneal -membrane to meet the transverse septum is the most popular hypothesis to explain diaphragmatic herniation. However, using SEM techniques [60, 61] we could not demonstrate the importance of the pleuro-peritoneal membrane for the closure of the so-called pleuro-peritoneal canals (Fig. 2.11).

It is still speculated, that delayed or inhibited closure of the diaphragm will result in a diaphragmatic defect that would allow herniation of gut into the fetal thoracic cavity. In a series of normal staged embryos, we measured the width of the pleuro-peritoneal openings and the transverse diameter of gut loops [68]. On the basis of these measurements we estimated that a single embryonic gut loop requires at least an opening of 450 μm size to herniate into the fetal pleural cavity. However, in none of our embryos the observed pleuro-peritoneal openings were of appropriate dimensions. This means that delayed or inhibited closure of the pleuro-peritoneal canal cannot result in a diaphragmatic defect of suffi-