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President of the Ulster Medical Society 1974–75

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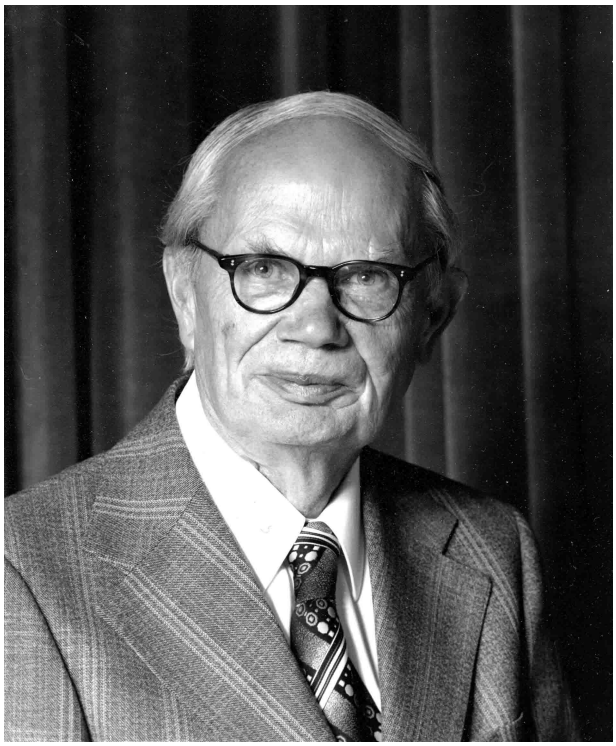
ONE ENTRANCE INTO LIFE

" For no king had any other first beginning;
But all men have one entrance into life
And a like departure."
The Wisdom of Solomon – The Apocrypha

OVER three-hundred and thirty years ago, just when England was about to be rent apart by the Civil War, Thomas Browne, a student of Padua and Montpellier and a Doctor of Medicine of both Leiden and Oxford, wrote *Religio Medici.* This contributed little to religion, but in the stately prose of a bygone age ranged far and wide with protestations of piety and a gentle irony. One of the best known passages is where he writes " . . . . and every man is some months older than he bethink him, for we live, have a being, and are subject to the action of the elements, and the malice of disease, in that other world, the truest microcosm, the womb of our mother". Tonight I would like to consider a few of the ways by which "the action of the elements and the malice of disease" may affect a man, be he future king or future beggar, before he is born and again while he is making the first adjustments to breathe air, that breath of life which in primitive animistic thought represented the beginning of his life.

In the older civilisations of the world, and even in recent times, men thought little of the miracle of normal development, but when a malformed and monstrous being was born reacted with admiration, awe or terror. Other disturbances of foetal and neonatal life were scarcely considered at all. Apart from a few descriptive studies it was only late in the last century that even malformations were studied in any scientific manner and the science of teratology developed and became integrated with the study of normal development. Until recently theories of causation were largely futile speculations over mere coincidences. Preyer in 1885 did report acute physiological experiments on the animal foetus, but available studies made no attempt to determine how the foetus lived in utero or could be exposed to the malice of disease before birth.



About the beginning of this century J. W. Ballantyne of Edinburgh with prodigious energy and dedication ranged far beyond descriptive studies of malformations and studied many intra-uterine diseases. Before the First World War the descriptive pathology of Germany excelled in the anatomical minutiae of malformations and also gave some useful descriptions of a few foetal diseases, such as congenital syphilis, and of the injuries and haemorrhages due to physical trauma at birth. In the decade before the Second World War careful surveys of foetal and neonatal deaths were started in Edinburgh by Dr. Agnes Macgregor, in Chicago by Dr. Edith Potter and in Boston, in the department of my former teacher, Dr. Sidney Farber.

In the published work before 1930 there is little of value for the understanding of disease in the foetus or newborn child and certainly little which even tries to go beyond the anatomical recognition and description of a few disease conditions. Almost the whole development of foetal and neonatal pathology has occurred during the years since I qualified, and it has been made possible by advances in foetal physiology pioneered in the thirties and forties by Sir Joseph Barcroft in Cambridge and by his disciples

now scattered over the world, and more recently by the studies of Geoffrey Dawes in Oxford. Concepts from the general biology of development have increasingly helped and developmental immunology and biochemistry is beginning to help. Despite the belief still mistakenly held in some centres, pathology is much more than the description and recognition of changes of structure in dead bodies and tissues. It is the recognition of the whole sequence of such disturbances as constitute disease, and to this the traditional techniques of tissue pathology have still much to contribute, but only if integrated with continuing advances in other disciplines. The advances made throughout the world in the pathology of this period of life have sometimes come from the thinking of men I have met and sometimes from those whose friendship I cherish. I have always looked backward over the territory conquered and forward to the frontier with a very special interest. For me the detailed story of these advances illustrates real co-operation in the world of science which transcends all national barriers.

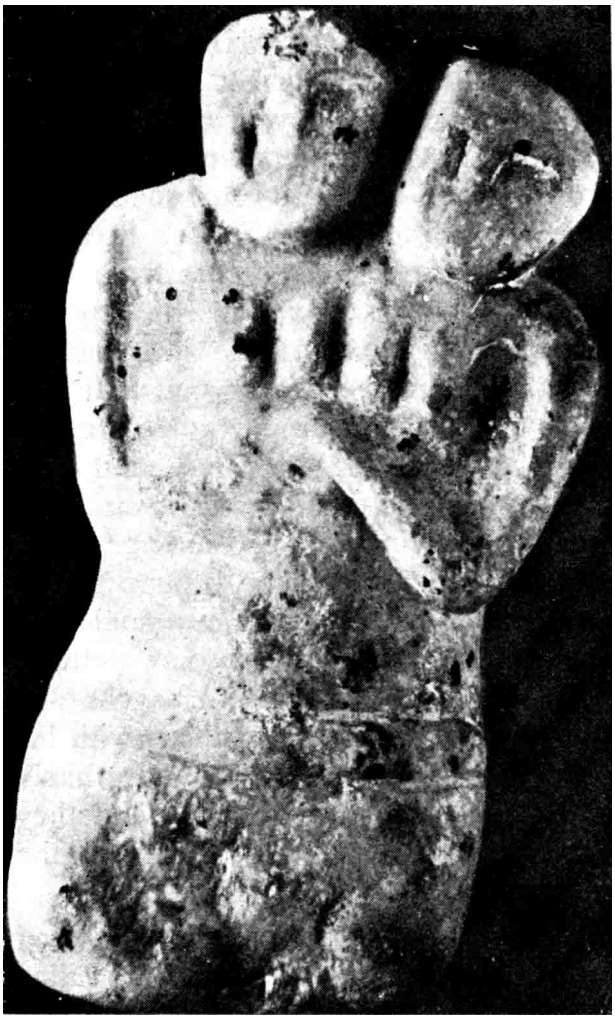


Fig. 1. *White marble figurine of double headed twin goddess from Anatolia approximately 6000 B.C. (Mellaart, J. (1963) Archaecology,* **16**, 29) *by permission.*

Congenital Malformations and Abnormalities

In the world of our forefathers, and up to at least the nineteenth century prayers for deliverance from pestilence and sudden death expressed a real and ever present fear. It was accepted as normal that about half of all children born alive should die in early infancy. The death of children before birth, the birth of malformed children who were almost certain to die, and the death of many children in the early days of life were thought inevitable. However, many views were held, especially about the more unusual and curious malformations. In ancient pre-Christian civilizations deformed children were often held to reveal the power and intentions of the gods, and the term monster means to show forth. Monsters were sometimes worshipped, and, if men made gods in their own image, they also often made them in these

Fig. 2. *Dicephalus dibrachius* (*Ahlfeld Atlas,* 1880).

Fig. 3. Janus from a silver Roman coin of the third century B.C.

monstrous forms. A figurine (Figure 1) in white marble from a neolithic site in Southern Turkey dates from 6500 B.C. and, like a chalk figure from New Ireland in the South Pacific and pre-Columbian sculptures from Mexico, shows a dicephalus dibrachius (Figure 2). These were not figments of the imagination. Janus was one of the oldest and most important of the native Roman gods. He had two faces (Figure 3). He presided over all beginnings in public and private life and was the god of all doors and gateways and portals, including the womb, and even Heaven itself. As the god of the opening of a new year he could look forward into the new and backwards into the old. The form of this twin faced god may be based on a variant of a cephalothoracopagus or diprosopus twin (Figure 4). The fearful Cyclops, blinded by Ulysses died at birth and had his nose above his single eye (Figure 5), a single cerebral hemisphere and

Fig. 4. Cephalothoracopagus twin (Ahlfeld Atlas, 1880).

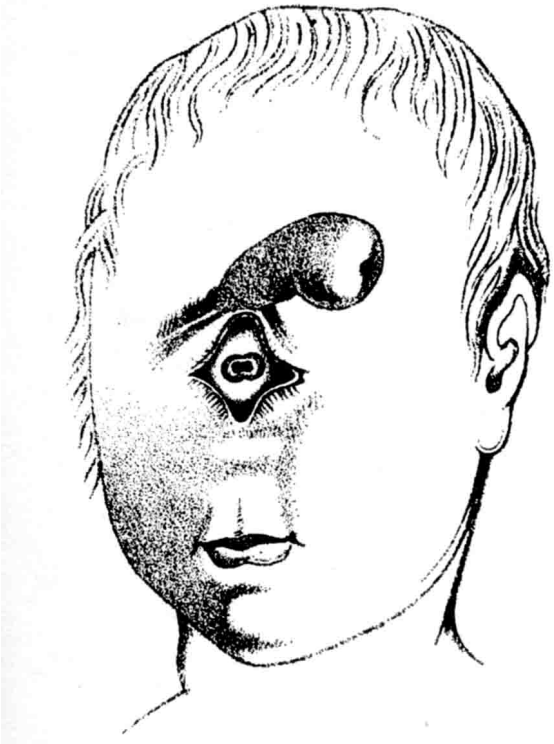


Fig. 5. Head of a cyclops monster (Ahlfeld Atlas, 1880).

an abnormal chromosome pattern. Atlas (Figure 6) with his crushing burden of the firmament of the Heavens was probably modelled on an occipital encephalocoele (Figure 7). Prometheus with his liver exposed to be torn by vultures may have been an exomphalos or more likely a gross gastroschisis. The great gods it was thought also liked to play, and they made monsters in fun or jest. In more recent times botanists have described the production of variants in

Fig. 6. Atlas carrying the Heavens. A drawing from a statue in Naples.

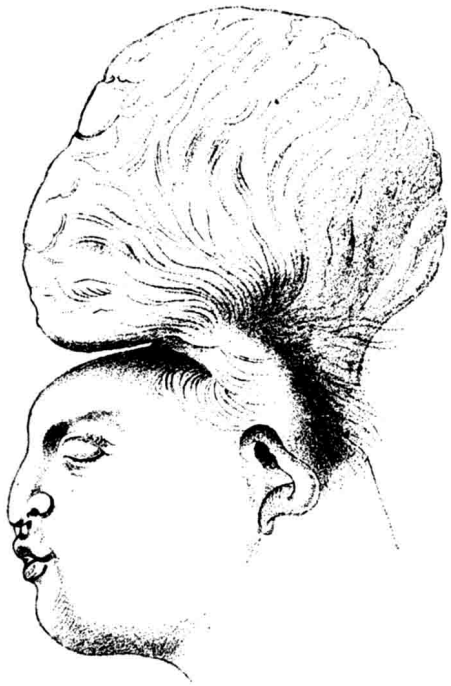


Fig. 7. An occipital encephalocoele (Ahlfeld Atlas, 1880).

nature by the term 'sport'.

In many civilisations malformed infants were venerated by astrologists as being sent from the gods to reveal the future. In the clay tablets of an Assyrian king ruling in Ninevah almost four thousand years ago there are long lists of malformations and their significance. Great calamities were foretold by the absence of nostrils, lips, tongue and anus, and great prosperity followed the birth of a child with three legs or an absent penis. In various forms other supernatural beliefs have persisted up to the present time, and deep within the minds of afflicted parents you may still find hidden fears and doubts, premonitions of disaster and ideas of punishment by an angry god.

In the Christian era, and especially when Christianity and the Church fought for the souls of men against residual beliefs in the old pagan gods and against witchcraft and devils, there was a greater tendency to ascribe malformations to evil spirits, to parental sin and even to bestiality. There are many painful episodes where good and scholarly men blinded by superstition acted unjustly. The learned anatomist Bartholin recorded objectively and without disapproval how in 1683 an unfortunate girl who gave birth to a child with a 'cat's head' was burned in the public square of Copenhagen.

The theory of maternal impressions represented a more humane belief. It flourished, especially in the seventeenth and eighteenth century and was accepted in some medical textbooks in America as late as 1889. An anencephalic child occurred because the mother saw a frog or a toad, a hare-lip followed a fright from a hare, and multiple bony deformities occurred because a mother watched a criminal broken on the wheel. This enormous and useless literature is a warning against retrospective study and the failure to observe controls, and yet wise and scholarly men discussed it in learned terms and believed in it, and perhaps it lingers still in the minds of some of our patients.

What conclusions can be drawn from the enormous volume of scientific work which up to now has been carried out on congenital anomalies? Certainly there is no single cause. Some are due to an inherited or genetic basis and sometimes Mendelian inheritance is evident. Dominant inheritance is usually manifest in trivial disorders often skeletal. Recessive inheritance is seen in a multitude of little

known metabolic anomalies. These are rare except in inbred populations. Some conditions appear more frequently in the general populations when the recessive gene involved has a high incidence. This occurs in cystic fibrosis of the pancreas where a gene carrier incidence of 1 in 20 gives an incidence of 1 in 1600 on chance mating. Since there is high penetrance the usual recurrence rate for a Mendelian recessive of 1 in 4 is found in sibs. In many anomalies, such as congenital pyloric stenosis, hare lip and anencephaly and spina bifida a statistical study will show clustering in kindreds suggesting a contribution from multiple genetic factors. This is multifactorial or polygenic inheritance. However, to have the genetic inheritance expressed requires a large contribution from unknown environmental influences. Even like twins with identical genetic inheritance and apparently very similar intrauterine environment may show one affected and one normal baby. Such lack of concordance in like twins shows how subtle may be the environmental influences modifying any genetic inheritance. Gross anomalies of chromosomes recognisable by existing methods are, as will be suggested later, relatively much more important in causing foetal loss early in pregnancy.

Many different agents, mostly chemical and physical, have produced malformations in experimental animals and often in doses far in excess of what the human foetus would ever encounter. Rubella and thalidomide are the best known agents in man, but even with all other known environmental causes they are numerically unimportant. The problem is far more complicated than the production of an arrest of development by the agent acting at a period and stage critical for the development of the region or part affected. Agents may produce anomalies in one strain of animals and not in another, and many environmental agents, known and unknown, may be powerless on their own, but may act if the genetic background is favourable. We must search carefully for any such environmental factors as can determine the expression of defects which are preconditioned by genetic factors. We can at present perhaps hope to control some environmental factors, but not our genetic inheritance. This search for facilitating or conditioning factors in the environment is the only present hope of reducing the toll of congenital defects. It is also not realistic to demand a guarantee that any drug is entirely safe and inert and will not influence the expression of some hidden genetic trait in some individual. The relationship between certain skeletal defects and such environmental influences as those exerted by thalidomide was relatively direct and the drug and not the genetic background was important. The disasters produced by this drug received disproportionate and unbalanced publicity. Let us hope that any discovery of other and less direct relationships will be treated by the lay press and pressure groups with more appreciation of the whole tragedy of congenital disease in general. These great human problems go far beyond medicine but are not advanced in courts of law or by clever legal and journalistic minds pleading special cases.

Wastage Before Birth

Basic to all understanding of disordered reproduction is an appreciation that from the very beginning the developing ovum or embryo may be malformed, and whether malformed or normal often dies. In this study of unsurpassing difficulty tribute must be paid to Arthur Hertig of Harvard University. Though a pathologist, he was also trained in the classical school of embryology of the Carnegie Institute of Washington. With the gynaecologist, Dr. Rock, he studied uteri removed from women of known fertility where the clinical history suggested that opportunities for conception immediately before operation were highly favourable. By irrigation of tubes and uteri and by searching with the binocular microscope he found eight ova before implantation and of these only four were adjudged normal. Implanted in the uterus before the time of the next menstrual loss he found 26 early ova and considered 9 were abnormal. He considered it probable that in any one menstrual cycle, and with 100 previously fertile women exposed to optimal conditions for conception, 42 failed to fertilise or failed to implant a fertilised ovum and 16 implanted a recognisably abnormal ovum which would often be lost without the women being conscious of anything but a slightly delayed period. Forty-two women missed a period because they implanted an apparently normal ovum. It is accepted that 15 to 25 per cent of recognised pregnancies abort in the first trimester. Many of these, and all abnormalities recognisable at birth, are derived from those implanted as apparently normal ova. Hertig's figures cannot be precise but are illustrative of early pregnancy wastage and comparable with observations in animals.

It would be interesting to discuss possible causes of this high loss of ova and embryos. Possibly the age of the female sex cell at ovulation is, as suggested by Hertig, one factor. Undoubtedly chromosomal and genetic factors are important even from the earliest cleavage stages. They are certainly important in

abortions in the early months of pregnancy. At birth chromosomal anomalies cause only 3 or 4 of every 1000 abnormalities, but they cause about 4 of every 10 spontaneous and recognisable abortions occurring in the first three calendar months. The distribution of this relatively high incidence of abnormal chromosome patterns in abortions is illustrated in such data as is given in Table 1. Only a few of the less severe chromosomal anomalies escape abortion and are born as malformations.

Table I
The incidence of various chromosomal anomalies in early abortions and in live births and showing the high abortion rate. Table from Smithells, R. W. (1971). *The prevention and prediction of congenital malformations in* Scientific Basis of Obstetrics and Gynaecology *by permission of the publishers Messrs. Churchill, London.*

	Frequency per 1000 *in*		*% Aborted (assuming* 20% *abortions)*
Karyotype	*spontaneous abortions*	*viable infants*	
XO ('Turner's syndrome')	55	0.4	97
Triploids and tetraploids	55	0	100
Trisomy G (mongolism)	25	≤2	80
Trisomy E	33	0.5	95
Trisomy D	30	0.25	97
Trisomy A, B, C, F	20	0	100

This evidence from chromosomal studies of a high loss of abnormal embryos is interesting because we suspect that a major proportion of all embryos abnormal for any cause are lost in the early months of pregnancy. Spontaneous abortions rarely yield material suitable for the recognition of these malformations, but there is another piece of evidence. In Japan legalised abortions have been permitted since 1952, and a dedicated group in Kyoto University have been able to obtain embryos of the second and third month which are less damaged than they usually are. The numbers are small, but for the anomalies studied the incidence of malformation in early pregnancy is considerably higher than at birth (Table 2) There must be a high wastage rate for abnormal embryos, and they must contribute largely and disproportionately to spontaneous abortions. The apparent excessive loss of those with minor anomalies, such as hare lip and polydactly, suggests that often minor structural anomalies are linked to other less evident defects highly detrimental to intra-uterine life.

TABLE II
The ratio of malformations found in legal abortions to those present at birth. Calculated from data of Nishimura and others (1968). *The numbers involved do not allow of any statistical significance.*

Embryo / Infant Ratios		
Exencephaly / anencephaly	3 : 1	
Myeloschisis	9 : 1	
Cyclopia	40 : 1	
Hare lip	9 : 1	
Polydactly	9 : 1	

There are maternal causes for spontaneous abortions and for apparent infertility, and these may cause much distress to many families, but it is fortunate that so many malformed products are eliminated by abortion. Recently pre-natal diagnosis in the early months of gestation has allowed recognition in high risk families of a few other infants with congenital anomalies, some with chromosomal anomalies such as the Down syndrome, others with various rare metabolic anomalies, and now even anencephaly. For some it may be a moral question whether these should be electively aborted. Even if they were all to be so destroyed it would be only a tiny fraction of those eliminated spontaneously.

OTHER ASPECTS OF INTRA-UTERINE LIFE

I have dwelt too long on congenital anomalies, but they are the largest single problem in the pathology of reproductive failure. There are many other aspects of intra-uterine life we might discuss. There is the central question of how the placenta, which immunologically is wholly foreign to the mother, is not rejected like any other foreign organ. There lies a secret central to the whole problem of kidney, heart and other transplants. There is the problem of how the placenta so different in structure in different animal species oxygenates and nourishes the foetus and of how disturbances in this may be recognised by histological or biochemical techniques. There are the fascinating studies of the complex factors which determine intra-uterine growth retardation. In the Western world this is not, as some of our social reformers would have us believe, a question of deficient maternal nutrition. It is very complex and in our society today it is an interesting fact that many more babies are underweight because their mothers have smoked than because their mothers have not had an adequate diet. Twins, like and unlike, are for the biologist a subject of increasing importance, and with like (one egg) twins there can be a wide

difference in birth weight and the possibility that one twin may steal the life blood of the other. Before and after birth there is the fundamental study of how infections reach the foetus and how the whole complex immune system matures and reacts against what is foreign. There is the unsolved problem of what determines the time of birth. From those babies born prematurely we are learning that they do not all develop at the same rate and that organs and tissue activities do not always mature in the same order. Ashley Weech was a stimulating leader of the group in the Children's Memorial Center in Cincinnati in the forties. He studied individual variations in the maturation of enzyme systems responsible for the postnatal elimination of bilirubin through the liver cells. He appreciated the significance of individual biochemical differences in liver cell function among infants of apparently the same maturity for the occurrence of so-called 'physiological jaundice'. We have long looked for individual variations in structural maturity of the lungs and hoped they might explain why some infants of a given maturity survived and others died. It is only in recent years that the biochemists are showing us that here also the variation is biochemically mediated. Tissue and biochemical maturation and the factors influencing it are important as we pass on to consider the initiation and maintenance of respiration.

The Breath of Life

With backward glances into development during intra-uterine life I want to look briefly at the greatest adventure of every mammal – the attainment of extra-uterine respiration, and the co-ordination of development in the respiratory, nervous and circulatory systems which makes that possible. Survival into post-natal life is dependent first on a development of lungs sufficient to maintain air breathing, on nervous mechanisms controlling this breathing, and on profound changes in the circulation from a foetal to a post-natal pattern. Many other activities and adaptations are required later, but the breath of life is the first necessity for life outside the womb.

Anatomically the lungs in utero are filled with fluid and are often expanded to a degree very comparable with that after breathing air. Lung tissue can develop without a communication with the surface, as when the trachea is absent. For a long time pathologists have recognised that a large amount of amniotic sac debris, squames and fat from the foetal skin, are sometimes present in the air spaces in stillborn and newborn babies. This is taken to indicate inspiratory gasping strong enough to draw fluid through the air passages and to indicate an episode, or episodes, of serious foetal distress. However, an episode of anoxia occurring after the membranes have ruptured and when the amniotic fluid has drained away will not be revealed in this way. There has been a long debate as to whether the foetus normally makes other respiratory movements before it is born. There is now good evidence that rapid movements involving the diaphragm and the intercostal muscles occur for long periods before birth. They have been extensively studied in sheep and in the human by Dawes and his team in Oxford. Undoubtedly, despite previous scepticism, they have been felt by some women and recognised by some obstetricians. The muscular apparatus of respiration is well exercised before birth. These rapid movements of the respiratory muscles, and even irregular single and stronger movements superimposed on them, do not move the fluid filling the air space system through the dead space of the trachea and bronchi. They are not related to anoxic conditions in the foetus, but in severe asphyxia they are replaced by strong gasping movements which may draw liquor and debris into the lungs.

There must be debate as to how far any movements occurring in utero correspond to respiration. They must lack the reflex controls of post-natal respiration. An important factor in initiating and maintaining rhythmic breathing after birth is a mature nervous system responsive to the massive new inflow of stimuli from the external world and especially from the lungs and other receptors controlling the rhythm of respiration. We may recently have attained some new insight into physical and chemical conditions in the lung making aeration possible. A new challenge is the study of the nervous control of breathing and especially the pulmonary reflexes. We will never understand lung reflexes adequately until the complex of the brain stem respiratory centres has been unravelled, but at present we know little even of the lung receptors and of the peripheral and central chemoreceptors.

Fish make do with a cardio-vascular system by which blood passes in parallel circuits through the gills and through the body tissues. Even in amphibians and reptiles there is no complete separation in the heart of blood from the body from that from the lungs. The body tissues can thus never receive fully oxygenated blood, but the rapid movements of most fish suggest the system is moderately efficient. It has to suffice for the mammalian foetus, where the placenta can be

equated with the gills, though there is a beautiful adaptation by which the foetal brain receives the best oxygenated blood. Normally the foetus in utero does not suffer from oxygen want, and we now know that terms such as 'Mt. Everest in utero' were based on measurements which emphasised only the variable but narrow margin of reserve of the placenta to any disturbance. With warm blood the birds and mammals attain the more efficient system by which all the blood after passing round the body is then passed to the lungs and oxygenated before being recirculated through the body. The newborn attains this perfected system virtually at the moment of birth by closing the ductus arteriosus by a mechanism still debated and by certain haemodynamic pressure changes, consequent to this and to the opening up of the blood vessels of the lung.

We must now come to the preparation of the lungs for the breathing of air and for nearly thirty years this has seemed to hold the secret to what I regard as the central problem of perinatal pathology. Can findings in the lungs explain why many infants are bom alive with a beating heart but fail to establish respiration, or more often establish respiration for a time, but in hours or at most days die with progressive respiratory distress and yet show no primary anatomical lesions in the lungs or other organs? Clinically this is the respiratory distress syndrome, and, with or without associated hyaline membranes in the lungs, it is responsible for nearly 40 per cent of neonatal deaths and now shares with congenital malformations major responsibility for neonatal death. I could weary you with how the simple branching tubules of the air spaces become increasingly complex and could illustrate this with histological sections or neoprene casts. I might describe how elastin develops in the air space walls and may help to prevent over-expansion of some spaces and resultant collapse of others. I would have to admit that in the walls of the terminal air spaces the development of elastin only becomes significant in the weeks and months after birth. We could discuss the lining cells of the air spaces and how increasingly blood vessels come into close contact with the potential air spaces. Some babies, usually under 28 weeks maturity, are obviously not structurally mature enough for independent life. Nearly thirty years ago I satisfied myself that structural maturation of the lung was not to be correlated closely with foetal age, weight or length. However, I think all would now agree that despite enormous study and research no recognisable structural deficiency and no anatomical immaturity can serve as the basis for these deaths,

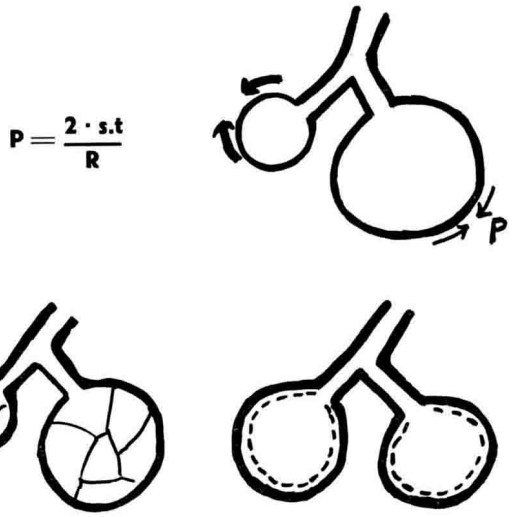


Fig. 8. If surface tension remains constant the formula shows that the pressure resisting expansion of the air spaces is high when the spaces are collapsed; as they expand it diminishes and allows over expansion. Elastic or other structures in the wall are insufficient to control this. A surfactant film alone allows uniform expansion.

many of which occur around 35 weeks.

In the late 1950's it became increasingly apparent that lung structure alone was not adequate for air breathing if the surface tension forces usual at air-fluid interfaces operated without modification in the terminal air spaces (Figure 8). Surface tension forces would resist the expansion of these small spaces by air, but as they expanded the force would weaken. Tissue structures, such as elastin, would be inadequate to prevent the resultant over-expansion of some air spaces and the further collapse of any poorly expanded neighbours. Again towards the end of expiration the walls of the spaces opened by air would be pulled together by surface tension forces and each new inspiration would require the effort of the first. A physically unique substance, designated surfactant, was discovered which reduces the force of surface tension in minimally expanded air spaces and allows them to expand readily. As spaces expand with air the surfactant in their air-fluid film increases the surface tension and so prevents over-expansion. It also prevents them collapsing completely as they again become smaller on expiration. It is the presence of this substance which makes air breathing possible, and in all air breathing animals it develops in the lungs only as term approaches. In man it develops probably by at least two chemical pathways, one appearing early but markedly subject to depression by

adverse influences such as anoxia, and the other developing rapidly around 35 weeks. Certain inclusions in the cells lining the air spaces may indicate its manufacture, but its study is still essentially a biochemical one. In the foetus it leaks into the amniotic fluid and the level there gives some indication of the preparedness of the foetus for extra-uterine life. The obstetrical department of this school developed one of the methods used to assess this. There is evidence that it reaches critical levels earlier under certain conditions, as in toxaemic babies and in those with prolonged rupture of the membranes. Its appearance is retarded in other states such as erythroblastosis and in the babies of most diabetic mothers. It thus seems that its delayed maturation is not simply a genetic or inborn bio-chemical immaturity, but is dependent at least in part on environmental factors operating on the foetus. Continued production is necessary and factors such as anoxia before, during and even after birth can reduce surfactant levels. Deficiency results in the respiratory distress syndrome. When there is deficiency of surfactant the pressure required to re-open air spaces during each fresh inspiration is raised approaching that of the first inspiration. Perhaps, because of the high negative pressure created within the air spaces as the infant struggles to aerate them fluid of high protein content escapes from capillaries and sometimes forms hyaline mem-branes. Many small air spaces remain collapsed and non-aerated and in these anoxic areas of lung the production of surfactant remains depressed and blood passing through them is not oxygenated. Whether maturation of surfactant can be usefully accelerated in man by glucocorticoid administration to the mother may still be debated. It does seem that synthesis is rapidly stimulated by birth, and if the infant with a deficiency can be kept alive for four to five days adequate levels will appear, and here the techniques of continuous positive pressure to the airways (C.P.A.P.) are proving valuable.

There are many other problems about the initiation and maintenance of respiration, and the recognition of surfactant and its mode of production is only one very significant advance in an area where for years little or no progress appeared to be made. Immediately after birth the lining of the lung air spaces is in direct contact with the highest oxygen concentration reached in the body. Especially when the infant is in an oxygen enriched atmosphere the lining cells may sustain direct damage. We have still the problem of how the flow of fresh stimuli from all over the body following birth immediately starts the well oxygenated infant to breathe and what chemoreceptors and reflexes maintain and control breathing. Some asphyxiated babies only gasp as chemical influences operate directly on lower medullary centres or through peripheral receptors, and almost with their dying gasp some of these fight their way back to life or are resuscitated after prolonged failure to breathe. What are the consequences, immediate or remote, of such severe asphyxia especially to the highly sensitive human brain? Much depends on how long oxygen deficiency has lasted in utero and on the maturity of the foetus. For many years large groups of workers have been studying this, and endeavouring to distinguish it after birth and throughout later life from the effects of prematurity itself and of toxic levels of circulating bile pigment and the outcome of developmental deficiency. Debate continues on its relative contribution to the heavy load of mental and nervous deficiency in the community.

The baby whose breathing is established is now ready to face other hazards which we as pathologists must study. Hazards of adaptations to post-natal nutrition and to metabolism independent of the mother present problems very different from those of adult pathology. The pattern of infection is distinctive with some organisms assuming a different importance from later life and with cellular and humoral immune mechanisms developing rapidly. More clearly than in the adult, pathology appears not as a rigid self-contained discipline but linked to all studies of life and living matter.

Lough Gill in County Sligo is the site of the lake isle of Innisfree. The Irish mystic and poet William Butler Yeats wrote of his wish to find peace there.

"I will arise and go now, for always night and day
I hear lake water lapping with low sounds by the shore;
While I stand on the roadway, or on the pavements grey,
I hear it in the deep heart's core."

Not far away on his tomb in the churchyard of Drumcliff there is the inscription written by him before he died –

"Cast a cold eye
On Life, on Death,
Horseman pass by".

The pathologist must study with cold detachment both life and death, and he of all men is constantly reminded that

" . . . all men have one entrance into life And a like departure."